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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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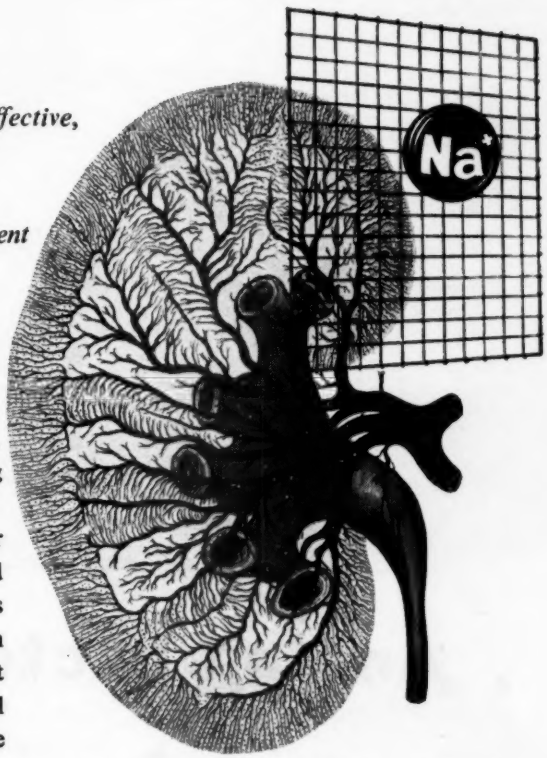

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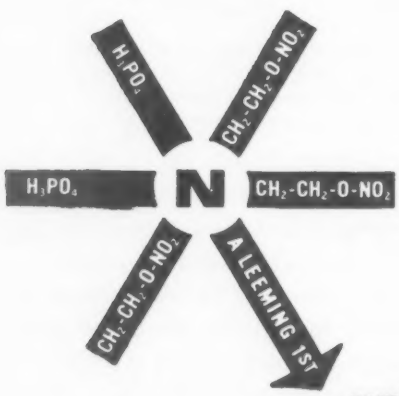

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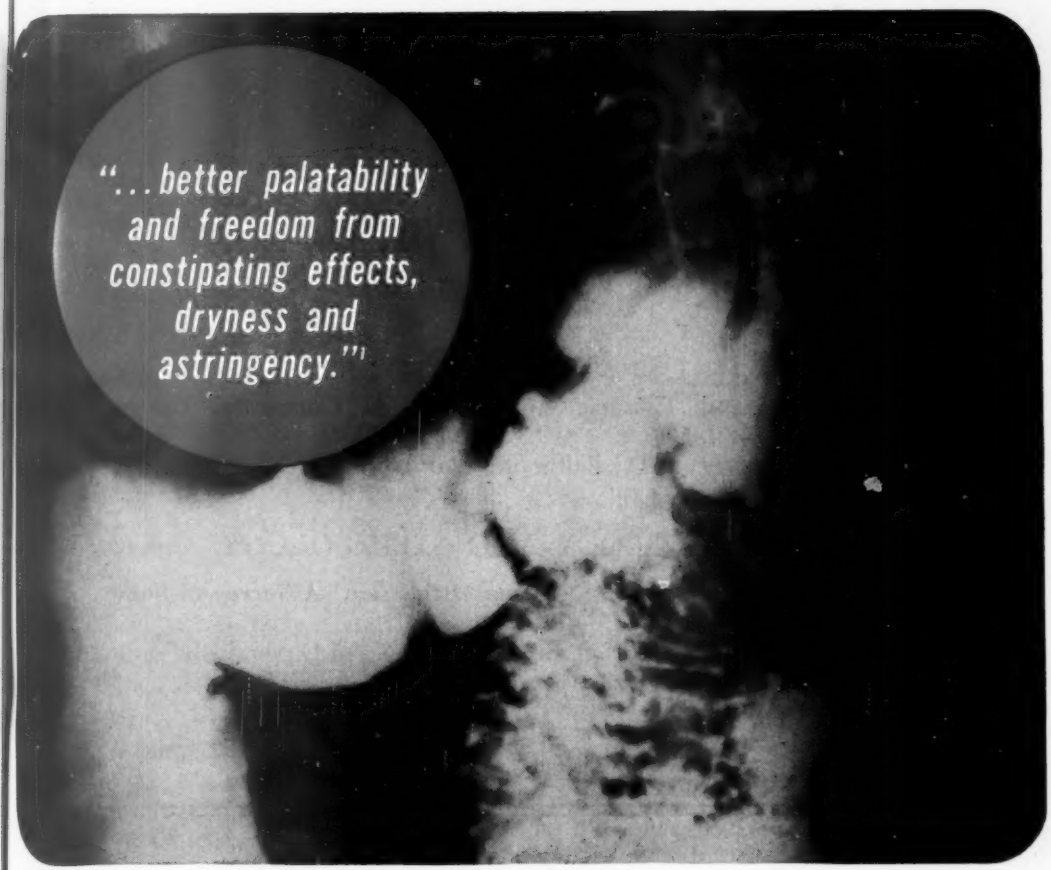

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1. Morrison, Samuel: Magnesium aluminum hydroxide gel in the antacid therapy of peptic ulcer, Am. J. of Gastroenterology 22:309 (Oct.) 1954.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1955

ORIGINAL ARTICLES

DANGERS OF INACTIVITY DURING AUTOMOBILE TRAVEL

By Alfred Soffer, M.D.

ELECTROCARDIOGRAPHER FOR THE GENESEE HOSPITAL

MEMBER, ATTENDING STAFFS, GENESEE AND ROCHESTER GENERAL HOSPITALS

(From the Heart Station of Genesee Hospital, Rochester, New York)

The tragic morbidity of the case presented could have been prevented had the subject utilized the two simple strategems of getting out of the vehicle more frequently to walk about and interrupting the trip to permit night repose in bed. The fact that the patient had been healthy previous to the trip suggests perhaps that no age group is exempt and that all of us who drive or ride should be mindful of the dangers of unrelieved automobile postures. Serious sequelæ have followed journeys of less than half a day's duration.

Presented below is the case of a 72-year-old woman who developed grand mal convulsions as a direct result of a long automobile trip.

Case Report. The subject is a 72-year-old woman who has always enjoyed excellent health. Complete physical examination and laboratory work disclosed no abnormalities previous to a trip to Florida. The bus trip to Florida took approximately 68 hours, and after a few days' rest the patient returned on a comparably long bus trip. The bus stopped at each meal time and for a rest period of 15 to 20 minutes between meals. The patient slept on the bus for each of the three nights of the trip. Towards the end of the trip the patient noted pronounced edema of both lower extremities from the knee to the ankle. The patient had never experienced edema of the legs before and she paid little heed to the swelling. Minimal swelling persisted upon her arrival home. Three days after her arrival, the patient's family witnessed a major grand mal convulsion which the patient experienced while seated at the breakfast table. Two other severe tonic clonic grand mal convulsions occurred within the next 18 hours and they were associated with emesis and followed by transient disorientation. The patient was immediately rushed to the Genesee Hospital. During her hospital stay spinal fluid, skull Roentgen studies and repeated neurological examinations disclosed no abnormality. Upon bed rest the edema of the lower extremities disappeared and the patient was made ambulatory in a few days. Since hospitalization and in the past 15 months the patient has experienced no neurological symptoms and no edema of the lower extremities.

Discussion. Vascular stasis was the inciting cause of the catastrophic episode in this 72-year-old female. The patient developed pronounced edema of the legs after sitting upright and relatively immobile during most of a 68-hour bus trip. This was followed within 3 days by a number of grand mal convulsions. Complete neurological, spinal fluid and Roentgen studies were normal, and though the patient has remained completely ambulatory she has had neither peripheral edema nor cerebral symptoms in the past 15 months. What occurred here in an exaggerated form is obviously related

to the cerebral ischemia (syncopal attacks) that occurs secondary to any permanent or transient state that permits excess pooling of blood in the lower extremities[2]. Prolonged bed rest is known to be associated with episodes of syncope during the period of ambulation. In the case described the efficiency of venous return reappeared when the patient was placed in the supine position for the first few critical days and then permitted to become ambulatory.

Homans[1] reports a number of instances of thrombosis of the deep leg veins due to long automobile rides. In one of these cases, a 56-year-old man, pulmonary embolization followed the appearance of the venous thrombosis. The role that the impedance to venous flow resulting from the bent knee position of automobile posture plays in these cases is yet to be determined.

There is an urgent message to be derived from these cases. More and more we have come to respect, both in fear and in gratitude, the potentialities of the lower extremities as circulatory reservoirs[3]. We are reminded that fainting during prolonged standing in one position, as a soldier must do on parade, occurs because of pooling of blood in the legs, which is attributable to the fact that the blood return to the heart is not aided in the usual manner by the massaging action of muscular movement. During automobile travel comparable orthostatic hypotension is much more likely to occur if circulatory abnormalities such as varicose veins already exist, but preexisting circulatory inadequacies are not necessary, as the history of this previously healthy subject demonstrates. It would be wise for susceptible travelers, that is, those with lower extremity venous abnormalities, to wear leg bindings during long automobile, railroad or airplane trips. Of paramount importance for all automobile travelers, however, is the necessity, demonstrated above, to get out of the car every few hours to walk about, if only for a minute or two. Passengers should move their legs frequently while riding. In the older age groups the earliest appearance of edema is a warning that the exercise periods are not frequent enough. A patient could then, for example, use the bus aisle for periodic walking. Leg bindings and occasional manual massage can be adjunctive prophylaxis. If these measures are inadequate to prevent edema or aching then the trip must be interrupted to permit bed rest in the supine or minimal Trendelenburg position. This is mandatory even if the bus possesses reclining seats, for it is not possible to raise the lower extremities to heart level by manipulation of the average reclining chair.

Summary. The case of a 72-year-old woman who developed grand mal convulsions as the result of a 68-hour bus trip is described. The peripheral vascular stasis which preceded this episode of transient cerebral ischemia has been responsible for a number of instances of thrombophlebitis or phlebothrombosis of the lower extremities with pulmonary emboli following automobile travel of less than half a day and may appear at almost any age. It is urgently recommended, therefore, that automobile drivers and passengers make frequent stops to permit maximum motion of the legs. In the older age groups, precautionary measures during prolonged automobile trips should include leg bindings, and if edema appears, the trip must be interrupted to permit rest in the supine position.

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STUDIES ON HERPES SIMPLEX VIRUS*
VI. OBSERVATIONS ON PATIENTS WITH RECURRENT HERPETIC LESIONS INJECTED WITH HERPES VIRUSES OR THEIR ANTIGENS

By Ernest Jawetz, M.D., Ph.D.
PROFESSOR OF MICROBIOLOGY AND LECTURER IN MEDICINE AND PEDIATRICS

M. F. Allende, M.D.

AND

Virginia R. Coleman, B.S.

(From the Departments of Microbiology and Medicine [Dermatology], University of California School of Medicine, San Francisco 22, California)

Recurrent herpes simplex is a frequent and frustrating disorder. The lesions are often neither large nor debilitating but they are highly irritating and annoying to patients, who demand tangible therapy and are rarely content to accept reassurance. Accordingly, a wide variety of treatments has been employed at different times. In a single volume of a dermatological journal there are articles proposing vigorously that a) all forms of herpetic lesions respond to repeated application of smallpox vaccine, b) many cases are not improved by smallpox vaccine but are cured by moccasin venom, c) severe and widespread herpetic lesions were "apparently cured by intracutaneous desensitization with autogenous blood serum withdrawn at the height of an attack" [8,19,20].

The mere coexistence of these and many more remedies suggests that all lack effectiveness. This is particularly evident in recurrent herpetic keratitis which often leads to blindness in spite of great therapeutic effort. Notwithstanding recurrent claims and therapeutic vogues, it seems justified to state that at present there is no sound, rational and commonly effective treatment available for recurrent herpes simplex[2].

The broad outlines of the natural history of infection with herpes simplex virus have become well established since the pioneering work of Burnet[7,17]. Infection is generally acquired in childhood. The primary disease is commonly a gingivostomatitis, sometimes a keratitis or vulvovaginitis. During primary infection the central nervous system may be invaded by the virus, giving rise to a meningoencephalitis which may sometimes be fatal[1].

Following initial infection a large majority of individuals are well and carry the virus in a latent form in skin adjoining mouth and nose, sometimes in other skin areas, or in the cornea. The virus may be brought into activity, and lesions precipitated, by a variety of trigger stimuli such as trauma, fever, ultraviolet radiation, emotional upsets, hormonal disturbance, and many others. In some persons, lesions occur only very rarely and only when provoked by a major stimulus. In others, herpetic

*Supported in part by grants from the Committee on Research, University of California School of Medicine; Burroughs, Wellcome & Company; and the National Institutes of Health (B 604).

lesions develop at frequent intervals and no definite trigger can be discovered.

In the course of the primary infection, the child (initial infection rarely takes place in adults) develops both antibodies to herpes virus and hypersensitivity to virus antigen which can be elicited by a skin test. The circulating antibodies produce what might be called "systemic immunity." This manifests itself in relative immunity to reinfection with virus from exogenous sources, (so that, at most, only a small local lesion develops), very rapid removal of virus introduced into the blood stream[11], and immunity to central nervous system involvement. These antibodies, however, seem to have virtually no effect on recurrence of local lesions in skin or cornea. Even in the absence of manifest recurrences of herpetic lesions following the primary infection, the antibodies to herpes virus persist for life, although fluctuating markedly from time to time.

During the past decade laboratory methods have become available which for the first time permit accurate quantitative laboratory studies in patients with herpetic lesions. It is easy to isolate the virus, establish a specific etiologic diagnosis, and accurately measure antibody concentrations. The virus can be adapted to various hosts and can be grown in quantity in eggs or tissue cultures. Virus particles can be concentrated and purified by high-speed centrifugation and separated from soluble antigens. The availability of these laboratory tools suggested reinvestigation of some of the puzzling aspects of latent and recurrent herpetic infection. Such studies have been in progress in our clinics and laboratories for some time[14,15,16].

At present, repeated vaccination with smallpox vaccine enjoys favor as treatment for recurrent herpetic lesions[9]. Originally this approach was based on the belief of an antigenic relationship between the viruses of herpes and of vaccinia[12], but this is not based on fact[2]. The occasional responses to this form of treatment can probably best be attributed to a nonspecific reaction[6] comparable to that following injection of a foreign protein, or of rabies vaccine[5].

More specific therapeutic efforts in patients with recurrent herpes simplex have included the repeated autoinoculation of skin with viable herpes virus and the administration of inactivated herpes virus from various sources[10]. This was done on the assumption that persons with recurrent herpetic lesions possessed only partial, or incomplete, immunity, which might be increased by re-infection or by repeated antigen administration. In one series of patients injected with formolized herpes virus in rabbit brain[10], 13 of 14 individuals were markedly improved, yet their antibody titer, measured with a crude neutralization test, appeared to remain unchanged. The injection of foreign protein or nervous tissue might have a similar but nonspecific effect.

With the availability of concentrated virus suspensions, viral antigens, and non-virulent strains of herpes virus, all of which could be administered to patients with ease and safety, it was decided to re-investigate the possible use of such materials in recurrent herpetic lesions. This paper reports on a 3-year study on more than 80 patients with recurrent lesions of the type commonly attributed to herpes simplex. While the therapeutic results are not spectacular the observations made on the natural history of the illness and certain laboratory studies are considered worthy of record.

Materials and Methods. PATIENTS. Eighty-six patients attended the special clinic set up for this study. Most of these individuals were

referred for special study because of lesions which recurred in spite of "conventional" therapy, including repeated smallpox vaccination and topical applications. Twenty-seven persons, mostly children, suffered primarily from recurrent herpetic keratitis with progressive opacification of the cornea. Thirteen had aphthous ulcers of the mouth which were of uncertain etiology, but probably not herpetic. The other 46 patients had herpetic lesions of skin and mucous membranes, often both, from which the virus could readily be isolated[2,17]. In addition to history and physical examination, the patients were skin tested with standard herpes antigen and normal allantoic fluid[16]. Blood specimens were obtained before, during, and after treatment. Herpes viruses were isolated on the chorioallantoic membrane of 12-day embryos 21 times in 27 attempts on 23 patients. All these patients gave positive skin tests, as did the majority of other patients with skin and mucous membrane lesions or keratitis. However, only 7 of the 13 patients with recurrent "aphthous ulcers" gave positive skin tests. This is in keeping with the finding of others, suggesting a non-herpetic etiology for these lesions[4,18].

NEUTRALIZATION TESTS. Sera were stored and neutralization tests performed *in ovo*, as described in detail in an earlier paper of this series[15]. Briefly, the test consisted in mixing serial dilutions of virus with a fixed dilution of serum previously heated at 56° C. for 30 minutes. The mixture was incubated at 37° C. for 1 hour, and then 0.5 cc. was injected into the yolk sac of 7-day-old embryonated eggs. The eggs were candled daily and embryos dying after 48 hours were recorded. This permitted the calculations of the 50% end point of death (LD50). The neutralizing ability of the serum was expressed as the difference in LD50 of virus-patient serum mixture and virus-normal control serum mixture. All sera from a given patient were tested simultaneously and in the same dilution, usually 1:30 or 1:50.

COMPLEMENT FIXATION. Tests were carried out in the conventional fashion, using 2 units of amboceptor, 2 full units of complement, 2% fresh sheep cells, and a fixation period of 18 hours at refrigerator temperature. The antigen consisted of whole allantoic fluid, from 12-day embryonated eggs infected with egg-adapted herpes simplex strain HR. The antigen was kept frozen at −20° C. until used. The results of complement-fixation tests are expressed as the reciprocal of the serum dilution giving $^{+++}$ fixation, in the presence of adequate controls. All sera from an individual patient were inactivated and tested simultaneously.

TREATMENT. Following clinical examination, skin tests, and initial blood specimen, most patients were given a course of 3 or 4 weekly subcutaneous injections of 0.5 cc. of one of the preparations described below. They were either observed 24 hours after each injection for local reactions, or were asked to record the appearance of the injection site in detail. Patients were also questioned as to systemic reactions but none was encountered in this study. After the initial course of injections a second blood specimen was obtained. In some individuals a second, or even a third similar course of injections was given at various times thereafter.

The following materials were employed:

a) *Concentrated suspensions of egg-adapted herpes virus.* Embryonated eggs were infected with the egg-adapted HR strain of herpes simplex virus by the yolk sac route on the 7th day of incubation[16]. Incubation was continued for 5 additional days at 36° C. and the eggs then refrigerated for 6 to 18 hours. Allantoic fluid was harvested, pooled, centrifuged lightly (1000 rpm for 10 minutes) and the sediment discarded. The fluid was spun at 12,500 rpm for one hour, and the supernatant pooled to be used for b) below. The sediment was resuspended in 1/20 the original volume of physiological saline and inactivated by ultra-violet irradiation as described previously[16]. Aliquots of the suspension were titrated for viable virus prior to inactivation. The material contained at least 95% of the total virus of whole infected allantoic fluid, usually in excess of 10^6 infective particles per cc. Prior to injection into patients, aqueous Merthiolate was added to the suspension in a final concentration of 1:20,000.

b) *Supernatant from infected allantoic fluid* centrifuged at 12,500 rpm for one hour, as described above. An aliquot from the pooled supernatant was titrated for viable virus and always contained less than 5% of the total virus concentration of whole allantoic fluid. However, the supernatant contained most of the complement-fixing antigen and of the skin-reactive material of allantoic fluid[16]. It was inactivated by ultra-violet radiation and distributed in rubber-capped vials with the addition of aqueous Merthiolate 1:20,000.

c) *Viable egg-adapted herpes simplex virus.* Three patients received whole allantoic fluid containing $10^{6.3}$ infective particles per cc. of strain HR. The material was freshly prepared as described under a) and tested for

bacteriological sterility, but was neither centrifuged nor inactivated.

Evaluation of Response. a) LOCAL REACTIONS AT SITE OF INJECTION. Patients were either observed 24 hours after an injection or were instructed to record carefully the size, erythema, elevation, and duration of the local reactions. Patients brought these records with them when reporting for their next injection.

b) EFFECT ON HERPETIC OR APHTHOUS LESIONS. Patients were questioned regularly about the frequency, size and duration of lesions and the associated discomfort or pain. Results were recorded as follows:

Definite improvement. The disappearance of lesions and freedom from lesions for a follow-up period of at least one year; or marked decrease in the frequency of lesions so that the usual interval between lesions would be prolonged at least threefold.

Questionable improvement. A subjective improvement, diminution in the size and discomfort of lesions, or a twofold increase in the interval between attacks, or both.

No improvement. Lack of any subjective improvement; no change in symptom-free interval.

Results. The immunizing ability of the three preparations employed for "treatment" was assessed in mice. When up to 10 consecutive injections (0.2 cc. each) of concentrated inactivated virus, or of supernatant, were given at 3 to 5-day intervals to mice, no appreciable resistance developed in these animals to intracerebral challenge infection with a neurotropic, mouse-adapted strain of herpes. However, the viable egg-adapted strain injected subcutaneously in 2 to 4 doses of increasing size gave partial, but appreciable, immunity to such intracerebral challenge[13].

The intracutaneous test injection of normal allantoic fluid, administered to all patients prior to their inclusion in the series, was designed to detect individuals with significant spontaneous hypersensitivity who might suffer serious reactions upon the injection of larger amounts of allantoic fluid. Only two such persons were found and they were excluded from the series.

The concentrated virus suspension elicited only a minor local reaction, with little edema or redness, but some induration about 48 hours after the injection. On the other hand, the supernatant or whole allantoic fluid containing viable virus resulted in marked local erythema, edema and tenderness in an area up to 5 cm. in diameter surrounding the site of injection. This reaction was maximal at 12 to 24 hours after injection, but sometimes continued for 2 or 3 days. In about three-fourths of the patients the initial injection of supernatant fluid or whole allantoic fluid produced the largest reaction. Successive doses resulted in progressively smaller responses. Not infrequently the last injection of a series failed altogether to evoke any reaction. The possible meaning of this observation is discussed below.

Only 50 patients could be followed satisfactorily for a sufficient period of time (at least one year after treatment) to permit inclusion in the series. This group included 17 patients with recurrent keratitis, 12 patients with recurrent aphthous stomatitis, and 21 individuals with recurrent skin lesions of herpetic etiology. The results of "treatment" are summarized in Table 1. With the exception of 3 patients injected with viable herpes virus (Table 3), most patients received initially a course of injections of concentrated, inactivated virus particles, later one or more courses of supernatant fluid. There was no discernible

difference in the patient's response to the different preparations, and consequently all results have been pooled. The number of patients in each group is not sufficient for meaningful statistical evaluation. Nevertheless, one gains the impression that the groups with definite herpetic etiology (keratitis and skin lesions) reacted fairly uniformly and behaved rather differently from those with aphthous stomatitis.

A comparison of the "definitely improved" and "not improved" patients in these two categories by the Chi square test is significant at the 90%, but not at the 95% level. Thus it might be tentatively concluded that whatever the effect of the injected preparations may have been in herpetics, it was clearly associated with improvement in them, as compared to cases of aphthous stomatitis. In view of the repeated demonstration[4,18] that recurrent aphthous stomatitis is often non-herpetic in nature, this group might be considered an inherent control in the present series. In comparison with the individuals with recurrent aphthous lesions who clearly failed to improve under "treatment," those with herpetic lesions reacted differently. Whether spontaneously, or under the influence of "treatment," the herpetic individuals showed a significant tendency to improve while under observation. The possible interpretation of this finding is discussed below.

In contrast to the earlier belief that in herpes-infected persons the level of antibodies remained constant[2], it is now established that marked variations in the concentration of neutralizing antibodies occur spontaneously[14]. These swings in antibody levels appear unrelated to the activity of herpetic lesions. The observations on the present series of patients again indicate the fluctuating level of neutralizing antibodies (Tables 2 and 3) to herpes simplex virus. Complement-fixing antibodies likewise have a fluctuating character. Neither of these antibodies appears to be significantly influenced by the injection of any of the preparations employed. In view of the poor immunizing quality of the nonviable virus concentrate or of the supernatant fluid, the lack of antibody response could be expected. However, it was surprising that viable virus preparations which possessed immunizing ability for mice likewise were without effect. This contrasted sharply with the changes in antibody titer observed in similar individuals who received a larger dose of virus intravenously. Geller *et al.*[11], found that the intravenous injection of 10^8 viable virus particles of the same egg-adapted HR strain provided a sufficient antigenic stimulus to raise the level of neutralizing antibodies significantly in 4 out of 9 patients.

The examples of neutralizing and

TABLE 1.—CLAIMED OR DEMONSTRATED IMPROVEMENT IN RECURRENT LESIONS FOLLOWING THE ADMINISTRATION OF HERPES VIRUS OR ITS ANTIGENS

Type of Recurrent Lesion	*No. Patients Followed*	*Definite Improvement*		*Questionable Improvement*		*No Improvement*	
		No.	*%*	*No.*	*%*	*No.*	*%*
Herpetic keratitis	17	8	47	7	41	2	12
Herpetic skin lesions	21	10	47	5	24	6	29
Aphthous stomatitis	12	3	25	2	17	7	58
Total	50	21	42	14	28	15	30

complement-fixing antibody titers shown in Tables 2 and 3 are representative of the entire series. The lack of antibody response applied equally to those patients who were obviously not benefited by the procedures and those who claimed, or were observd to show, marked and lasting improvement.

Discussion. In order to evaluate the effect of any therapeutic agent critically it is necessary to administer to alternating patients a placebo, that is, a substance which could not reasonably be expected to have a specific therapeutic effect. This was not done in the present study. An "internal" control was provided by the inclusion of a group of patients with recurrent apthous lesions who reacted differently from the group of patients with recurrent herpetic lesions. Thus it is possible to state that the therapeutic pro-

TABLE 2.—NEUTRALIZING AND COMPLEMENT-FIXING ANTIBODIES TO HERPES-SIMPLEX VIRUS IN THE SERUM OF PATIENTS INJECTED WITH ANTIGENS FROM HERPES-SIMPLEX VIRUS

Patient	*Serum Dil.*	*Treatment* No. of Inj.*	*Serum Obtained*	*Amount of Virus Neutralized (log)***	*Complement-Fixing Titer of Serum†*
Car . . .	50	–	9– 6–50	2.2	–
		4 Sed.	10– 3–50	2.4	20
		–	11– 7–50	2.0	20
		4 Super	11–29–50	2.8	10
Col . . .	50	–	9–28–49	1.9	80
		4 Sed.	10–26–49	2.3	80
		–	5– 3–51	1.5	160
Cra . . .	30	–	11–18–49	1.7	–
		6 Sed.	12–28–49	1.3	5
		–	9–19–50	1.3	10
		–	4– 5–51	1.6	20
		4 Super	5– 7–51	1.6	<5
Kon . . .	30	–	3–21–50	1.3	10
		4 Sed.	4–18–50	1.6	40
		–	8–22–50	1.5	40
		–	8–14–51	1.0	5
Kos . . .	50	–	1–24–50	1.4	20
		4 Sed.	2– 7–50	1.8	10
		–	3– 7–50	1.6	*Anticomp.*
		4 Sed.	11–19–51	1.6	*Anticomp.*
Wal . . .	200	–	5– 2–50	2.4	10
		4 Sed.	6– 6–50	2.3	10
		–	7–25–50	2.5	10
		6 Super	9–12–50	3.3	10
		4 Super	5– 3–51	3.0	5
		–	1– 9–52	2.4	5
Mar . . .	30	–	12–16–49	1.7	5
		4 Sed.	1–10–50	2.0	20
		3 Sed.	1–31–50	1.6	20
		–	1–10–51	1.6	5
		–	4–19–51	1.8	–
		–	11–28–51	1.6	–

* Sed. = concentrated suspension of herpes virus
Super = supernatant from infected allantoic fluid

** Log of LD50 in presence of normal rabbit serum, log LD50 in presence of patients' serum

† Reciprocal of serum dilution giving $^{+++}$ fixation

cedures employed had some, though admittedly limited, beneficial effect on herpetic patients. In addition, it is probable that this effect was not within the usual limits of the natural variation of the untreated disease because the large majority of patients had received other treatment, particularly repeated smallpox vaccination, before being referred to us. These patients continued to have regular, severe relapses before they came to us, but about half of the individuals with recurrent herpetic lesions were improved during observation at this clinic.

The natural history of "untriggered" frequently recurrent herpes often shows a spontaneous waxing and waning in the frequency of lesions. In the present series it was notable that the local reaction to successive injections decreased markedly in individuals who appeared to derive some benefit. Many such patients reported a striking decrease in painful sensations preceding and accompanying herpetic lesions and in erythema and swelling. They indicated that the lesions, when recurring, were minute and fleeting. It might be postulated that these persons were be-

TABLE 3.—NEUTRALIZING ANTIBODIES IN THE SERUM OF PATIENTS INJECTED WITH VIABLE EGG-ADAPTED HERPES-SIMPLEX VIRUS

		Treatment		*Amount of Virus*	
Patient	*Serum Dil.*	*No. of Injections*	*Date Serum Obtained*	*Neutralized (logs)**	*Complement-Fixing Titer of Serum**
Boo . . .	30	–	4–15–53	2.5	–
		–	12– 8–53	3.4	10
		–	12–28–53	2.7	40
		3	1–21–54	3.6	20
		–	3–15–54	2.9	–
Ros . . .	50	–	1– 5–54	3.4	20
		2	1–20–54	3.7	80
		–	5–24–54	3.1	–
Pre . . .	90	–	2–21–54	1.9	20
		3	3–19–54	2.4	40
		–	5–27–54	2.5	40

* See Table 1

What might be the possible beneficial effect of administering herpes virus or its antigen to persons with recurrent herpetic lesions?

a) The additional antigen administered might provoke a rise in concentration of circulating antibody, which might be able to reach the superficial epithelial cells where herpetic activity begins, and thus prevent recurrences. In the present study no rise in antibody titer was observed and, therefore, this possibility can be dismissed as a probable source of benefit.

b) The role of hypersensitivity in recurrent herpetic lesions is unkown. ing "desensitized" to herpes antigens and consequently had fewer or less severe lesions. This explanation is compatible with the results observed in this study.

c) The injection of herpes viruses, or their antigens, might only provide a nonspecific stimulus, comparable to any foreign protein injection, coupled with being a suitable vehicle for supportive reassurance by the physician. Many persons with recurrent herpes establish very rapidly a strong positive transference to the physician[3]. They are anxious to please, are cooperative, eager and submissive. Provided the

physician gives them strong encouragement, aided by a "new method of treatment," they often respond with a disappearance of lesions. When therapy is withdrawn, and with it the support of the physician, lesions may recur.

While this is undoubtedly a much over-simplified version of a complex psychosomatic picture, the results of the present series are, in part at least, compatible with it. Many of the reports dealing with recurrent herpetic lesions indicate that approximately half of the patients were improved by the procedure employed, no matter what its nature. Most of the patients referred to us had been given other forms of treatment but failed to respond to it, so that they probably constituted the "failure" half of the original group, seen by the referring physicians. Since the original treatment given to the original group undoubtedly was not specific for recurrent herpes and resulted in remission in about 50% of cases, it appears possible that another form of therapy applied to the "failure" half of the group might again result in remission in about 50% of cases. Thus the hypothesis might be proposed that none of the forms of treatment for recurrent herpes simplex, including the administration of herpes viruses or their antigens employed in the present study, have any specific curative effect. They might merely influence the patient as nonspecific physical irritants, serving as potent vehicles for psychological support.

The observed difference in response of the patients with recurrent aphthous stomatitis and of patients with recurrent herpetic lesions appears to be a real one. It is in agreement with the evidence for a non-herpetic etiology of aphthous stomatitis in many patients[4,18]. Evidently the impulses, physical, emotional or constitutional, which control the frequency of herpetic recurrences do not apply to the aphthous lesions of unknown etiology. To elucidate and attempt to influence the complex trigger mechanisms that call forth viral activity in the herpes-infected individual remains a formidable challenge. For the present, it appears likely that the small benefit derived by the patients with recurrent herpetic lesions was in part due to specific "desensitization" and in part to nonspecific irritation and strong suggestion.

Summary. A series of patients with recurrent herpes simplex of skin, mucous membranes or cornea, or with recurrent aphthous stomatitis, were injected with herpes virus or its antigens. These individuals had failed to improve with other conventional forms of treatment. About half of the patients with definite herpetic lesions were markedly improved, but few of those with recurrent aphthous lesions were benefited. None of the patients showed a significant change in their complement-fixing or neutralizing antibodies to herpes simplex virus. It is proposed that the limited beneficial effect of the preparations used might be, in part, due to desensitization with specific antigens, and, in part, due to the strong psychogenic impact of a "new treatment" on suggestible individuals.

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HEXAMETHONIUM, HYDRALAZINE AND RAUWOLFIA SERPENTINA THERAPY IN HYPERTENSION*

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In the past four years there have been many reports of the use of hexamethonium, hydralazine and *Rauwolfia serpentina* in the treatment of essential hypertension[4,7,8,10,13,15]. In order to evaluate for ourselves the effect of these drugs in patients with hypertensive vascular disease of varying degrees of severity, a clinic for hypertensives was begun 3 years ago. The total number of patients has been kept small, and they have been carefully selected and followed. This communication is concerned with the results of therapy in 66 patients.

Method. No patient was selected unless his diastolic pressure was consistently above 100 mm. of mercury. Patients with a known history of primary renal disease or an initial nonprotein nitrogen (NPN) above 70 mg. per 100 cc. were excluded (with two exceptions). The patients selected for treatment were divided into 4 groupings as follows:

GROUP I. The patients considered to have mild hypertensive vascular disease were treated with *Rauwolfia serpentina* alone. These patients would fall into Smithwick grade 1, or at most, grade 2.

GROUP II. The patients with more severe hypertensive vascular disease were given hexamethonium alone, or in combination with hydralazine and *Rauwolfia serpentina*. All but one patient had a fixed hypertension as well as organic changes in the heart, kidneys and optic fundi. Therapy was instituted while the patient was in the hospital.

GROUP III. Patients with "malignant" hypertension were treated with hexamethonium, hydralazine and *Rauwolfia serpentina*. The finding of papilledema was considered diagnostic of "malignant" hypertension. The first 2 patients in this group were markedly uremic when first seen.

GROUP IV. This group consists of 12 patients, previously treated by sympathectomy, whose diastolic hypertension persisted even in the standing position. These patients were treated with veratrum, hexamethonium, and *Rauwolfia serpentina* singly, or in combination.**

The patients in all of the groups were seen in the outpatient clinic at frequent intervals. The blood pressure was recorded at each visit in the reclining, sitting and standing positions. Recumbent pressures were taken after the patient had rested at least 5 minutes, and the pressures in the sitting and standing positions were then taken in quick succession. The diastolic pressure was taken at the point of disappearance of the Korotkow

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sounds according to the criteria of the American Heart Association[2].

All patients were advised to adhere to a diet containing no added salt. Therapy with reserpine (Serpasil, Ciba) was begun with a dose of 0.25 mg. twice daily for one to two weeks and then reduced to 0.25 mg. once a day. The largest dose used was 2.0 mg. per day. The largest dose of whole root (Raudixin, Squibb) used was 400 mg. per day, and the largest dose of extract (Rauwiloid, Riker) was 6.0 mg. per day. The initial doses of hexamethonium were small but after the first week more and more was needed to achieve a good blood pressure reduction. Hexamethonium was not given in excess of 875 mg. five times per day by mouth or 50 mg. five times a day parenterally. The patients taking hexamethonium were taught to take their own blood pressure, measure the dose, and several learned to give themselves injections of the drug. Pentapyrrolidinium (Ansolysen, Wyeth) was substituted for hexamethonium in a few patients after October 1, 1954.

A dose of hydralazine above 400 mg. per day was not given to any patient. After an early trial of hydralazine alone in severely ill patients, it was used solely in conjunction with hexamethonium and *Rauwolfia serpentina*. Hydralazine was begun several days to weeks after hexamethonium or *Rauwolfia serpentina* so as to avoid the undesirable tachycardia, headache and nausea it may produce.

In evaluating results, we have compared the average of the last 3 observations before therapy with the average of the last 3 observations while the patient received therapy. In a few instances, only 2 observations were averaged. The period between each blood pressure observation was at least one week. Unfortunately, the blood pressures taken in most of the hexamethonium-treated patients prior to therapy, were in the recumbent position only. However, because of the marked postural changes in blood pressure in patients treated with hexamethonium, all 3 positions (recumbent, sitting, and standing) are given, and are compared to the pretreatment recumbent value. The blood pressures were compared in the sitting position, only, in patients treated with *Rauwolfia serpentina* alone. The sitting position was chosen in order to minimize differences in resting time prior to the blood pressure determination, and to include at least part of any postural effect.

Results. GROUP I. The result of therapy in 26 patients treated with *Rauwolfia serpentina* alone for an average of 10.5 months is shown in Table 1. Twenty-four of the patients had mild hypertensive vascular disease. The remaining 2 patients had severe disease, but are included because they are now taking only reserpine with good result. Fourteen of the patients achieved a reduction of their diastolic pressure amounting to at least 15 mm. of mercury.

TABLE 1.—RAUWOLFIA SERPENTINA

Number of patients	26
Age (in years)	
Average	40
Range	18 to 54
Duration of therapy (in months)	
Average	10.5
Range	4 to 19
Sex	
Male	8
Female	18
White	14
Colored	12

AVERAGE BLOOD PRESSURE (SITTING) IN MM. OF HG

Before Treatment	*After Treatment*
195 ± * 20	173 ± 27
123 ± 11	108 ± 15

AVERAGE BLOOD PRESSURE CHANGE IN MM. OF HG

	Number of Patients
Systolic ↓ 20	16
Systolic ↑ 20	0
Diastolic ↓ 15	14
Diastolic ↑ 15	0

SIDE EFFECTS

	Number of Patients
Sleepiness	11
"Stuffy" nose	8
Weight gain	11
Psychiatric disturbance	2

* ± refers to one standard deviation.

Six of the patients who showed a good reduction in their blood pressure with therapy were placed on placebo for 6 weeks. Five of these 6 patients had complained, initially, of headache. Their headaches disappeared with therapy, but did not reappear while they took a placebo even though their blood pressure returned to the control level.

In this group of 26 patients there was one young, severely disabled victim of poliomyelitis followed for 7 months. Two other* such patients were followed for a short time only. In 2 of these patients there was a good reduction of blood pressure, namely 195/142 to 130/92, and 153/123 to 106/72 respectively. The third patient became somnolent and remained so even though the dose of reserpine was decreased to 0.125 mg. per day. When reserpine was stopped, the somnolence disappeared.

The side effects of *Rauwolfia serpentina* have been, for the most part, mild. (See Table 1.) Eleven patients noted sleepiness, and 11 had an increased appetite and weight gain. The weight gain was usually limited to the first few months after the beginning of therapy, and amounted to as much as 15 pounds in a few individuals. Approximately one-third of the patients complained of a "stuffy" nose. The bradycrotic effect of *Rauwolfia serpentina* was noted in almost all of the patients. Two patients experienced more severe effects. One man while being treated with reserpine had an episode of depression which was treated with electroshock therapy elsewhere. Another male patient complained that he felt "like jumping out of the window." After therapy with the whole root was stopped for a short time this feeling disappeared. Reserpine was started, and he has not had a recurrence of this difficulty. The appearance of any of the side effects did not necessarily coincide with a reduction in the patients' blood pressure.

Pyribenzamine hydrochloride (Ciba), 50 mg. three times a day, proved quite effective in combating the "stuffy nose." In those who complained of excessive sleepiness, the dosage of *Rauwolfia serpentina* was reduced.

GROUP II. The result of therapy in 19 patients with severe hypertensive vascular disease is shown in Table 2. These patients were, on the average, 5 years older than those in Group I and had been known to have hypertension for a longer time. All but one of these patients had left ventricular hypertrophy patterns on their electrocardiograms, and 8 had been in frank congestive failure on at least one occasion. All but 4 had some degree of renal insufficiency as shown by an abnormality in at least one of the following tests: phenolsulphonphthalein, (PSP), urea clearance, NPN, urinalysis. They have been treated with hexamethonium for an average of 14 months, and have received additional therapy with hydralazine and *Rauwolfia serpentina*.

Three patients, all Negro males, died while receiving therapy; 2 in congestive failure, and one following a cerebrovascular accident. Four patients are no longer being followed in our clinic. One was treated with sympathectomy and is doing well 1½ years later; one moved to California; one patient initially treated by Schroeder with good result has failed to return to the clinic after again achieving a good result; and in one elderly woman, treatment was stopped due to her age and she is now seen at infrequent intervals in another clinic.

Constipation, postural hypotension,

*These patients were studied through the cooperation of Dr. George Saxton and Dr. Angelo Creticos of the Respiratory Rehabilitation Center.

dry mouth and blurred vision are almost universal complaints of patients taking hexamethonium. As a result, only one-fourth of this group have continued taking hexamethonium by mouth. Several men complained of impotence and difficulty in urination, and a few complained of intolerance to cold. Urecholine, in small doses, has been ineffective in controlling any of these undesirable effects of hexamethonium. Recently, *Rauwolfia serpentina* has been added to the regimen of these patients and several have reported less constipation and the need for less hexamethonium while maintaining a good reduction in their blood pressure. However, most of the patients continue to resort to milk of magnesia and cascara on frequent occasions. Dry mouth, blurred vision and impotence in the male have not been alleviated except by discontinuation of the drug. One patient, while taking hydralazine alone, developed generalized edema and questionable arthralgia, which disappeared when hydralazine was stopped. Otherwise, we have not seen the rheumatic, febrile syndrome described by Morrow *et al.*[9] and by Dustan, Corcoran, Taylor and Page[3].

TABLE 2.—HEXAMETHONIUM

Number of patients	19
Age (in years)	
Average	45
Range	33 to 58
Duration of therapy (in months)	
Average	14
Range	3 to 33
Sex	
Male	12
Female	7
White	12
Colored	7
Left ventricular Hypertrophy (ECG)	18
Congestive failure	8
Sympathectomy prior to therapy	3
Lost to series	4
Died (all Negro male)	3

AVERAGE BLOOD PRESSURE IN MM. OF HG

	Before Treatment	*After Treatment*
Recumbent	219 ± 25	194 ±* 18
	133 ± 8	120 ± 13
Sitting	———	180 ± 19
		115 ± 11
Standing	———	174 ± 19
		108 ± 28

CHANGE IN BLOOD PRESSURE IN MM. OF HG

	Number of Patients		
	Recumbent	*Sitting*	*Standing*
Systolic ↓ 20	10	14	14
Systolic ↑ 20	0	0	0
Diastolic ↓ 15	9	12	12
Diastolic ↑ 15	0	0	0

* ± Refers to one standard deviation.

Case Reports. The case histories of 2 patients in whom a good result has been achieved are as follows:

G.B., #38–89–50, a 46-year-old white housewife with an 11-year history of hypertension was admitted due to episodes of paroxysmal dyspnea. One year before she had an episode of acute pulmonary edema. Six months before admission her basal metabolic rate was recorded as plus 63% and a subtotal thyroidectomy was performed in another hospital.

Physical examination on admission revealed a recumbent blood pressure of 208/112 and Keith-Wagener Grade II changes in the optic fundi. There was moderate cardiomegaly.

The laboratory findings included a left ventricular hypertrophy pattern on the electrocardiogram. The urine contained no albumin, and the specific gravity was 1.015. The NPN was 48 mg. per 100 cc. and the maximal urea clearance was 21.8 cc. per minute.

In the hospital she had 2 episodes of pulmonary edema and was digitalized. Several histamine, Regitine, and benzodioxane tests were of equivocal significance and retroperitoneal pneumography failed to reveal any adrenal tumor. Hexamethonium therapy was begun in the hospital, and the patient has continued taking parenteral hexamethonium,

15 to 25 mg. three to five times a day. Hydralazine was added after 6 months, and reserpine after one year. Now, 2 years after the beginning of therapy, the blood pressure recorded in the outpatient clinic on the last visit was 230/130 recumbent, 170/110 sitting, and 170/98 standing. Because her blood pressure at home (sitting) was below 170 systolic most of the time, she decreased the amount of hexamethonium to 10 to 20 mg. once or twice daily. Occasionally she feels "winded," but there has not been any recurrence of paroxysmal dyspnea or of dependent edema. She has not taken any digitalis for 8 months.

R.McM., #38–70–66, a massive Negro carpenter, was first admitted to the hospital in December, 1951, with the complaints of exertional dyspnea, pedal edema, repeated epistaxes, and episodes of substernal pain of 2 years' duration. He had known of his hypertension for 4 years.

Physical examination on admission revealed a recumbent blood pressure of 264/170 but later, in the hospital this was observed at 220/130. Keith-Wagener Grade II changes were seen in the optic fundi. The heart was enlarged to the anterior axillary line; the aortic second tone was booming, and there was a Grade III, harsh, apical systolic murmur.

The urine showed 1 plus albuminuria and a specific gravity of 1.026 on a random sample. The NPN was 38 mg. per 100 cc. A PSP test showed 22.5% excretion of the dye in 15 minutes, and 57.5% excretion in 2 hours. A left ventricular hypertrophy pattern was present on the electrocardiogram. The blood pressure fell from the control value of 244/140 to 180/100 with sodium amytal.

He was given a reducing diet containing no added salt, phenobarbital gr. ¼ t.i.d. and was discharged. For the next 4 months he worked 8 hours daily but noted increasing fatigability, and insomnia, several episodes of epistaxis and substernal "tightness."

Upon readmission in April, 1952, the recumbent blood pressure was 230/150 and there were now a few hemorrhages and exudates in the optic fundi (Keith-Wagener Grade III). Hexamethonium and hydralazine were begun and the patient was digitalized. For the next 11 months the patient took 40 mg. of hexamethonium intramuscularly 5 times a day, and hydralazine, 100 mg. q.i.d. orally. In March, 1953, during a prolonged period of nausea, obstipation, and headache he was again admitted to the hospital. There was now 4-plus albuminuria, and several observers felt that there was early papilledema. Inadvertently, he was changed to oral hexamethonium, but after frequent episodes of weakness, dizziness, and severe constipation, parenteral hexamethonium was restarted in October, 1953. After starting reserpine in April, 1954, constipation became much less of a problem. In December, 2½ years after the beginning of hexamethonium therapy, the blood pressures recorded in the outpatient clinic were 220/140 recumbent; 160/110 sitting; and 150/108 standing. The optic fundi were classified as Keith-Wagener Grade II. The patient feels well, and works 8 hours daily without dyspnea or dependent edema.

GROUP III. Hypertension with papilledema was considered diagnostic of "malignant" hypertension[12]. The result of therapy with hexamethonium, (and "Ansolysen"), hydralazine, and *Rauwolfia serpentina* in 13 patients is presented in Table 3. The initial NPN in

TABLE 3.—HYPERTENSION WITH PAPILLEDEMA

Number of Patients	13
Age (in years)	
Average	37
Range	18 to 52
Sex	
Male	6
Female	7
White	9
Colored	4
Left ventricular hypertrophy (ECG)	12
PSP excretion 15% in 15 minutes	7 (of 11 tested)
Blood pressure on admission (in mm. of mercury)	
Average	$\frac{233 \pm^{*} 42}{146 \pm 19}$
Died	7
Duration of therapy (in months)	
Average	2
Range	¼ to 4
Living (All white)	6
Duration of therapy (in months)	
Average	9.7
Range	3 to 18

* ± Refers to one standard deviation.

2 of these patients was above 140 mg. per 100 cc. but such markedly uremic patients were thereafter excluded.

The effect of the factors of race, sex, and renal function on the mortality is striking, even though not statistically significant in such a small group. Of the 6 patients still living 5 are white females who had a normal or only slightly elevated NPN initially, and one is a white male. All of these patients had mild albuminuria, up to 2+ by gross testing. The PSP excretion was 10% in 15 minutes in 2; 15% in 15 minutes in 2 and 20% in 15 minutes in the last 2.

All 4 Negro patients in this grouping were male, and all 4 died, even though 2 of them had a near normal NPN when first seen. The other 3 patients who died included two white females and one white male. The white man who died maintained an NPN of 53 to 64 mg. per 100 cc. and a good reduction in his blood pressure for 2 months. Papilledema, however, persisted, and he died suddenly of an unexplained, massive, pericardial effusion. Necropsy also revealed extensive vascular changes in the kidneys, brain, and heart. Of the 2 women who died, one had 4-plus albuminuria and a PSP excretion of only 18% in 2 hours, but her NPN was only 43 mg. per 100 cc. She lived in the hospital for 4 months, with the terminal event being bronchopneumonia, and massive pleural and peritoneal effusions. Necropsy also revealed advanced arteriolar nephrosclerosis and malignant nephrosclerosis. The other woman who died had 4-plus albuminuria, an NPN of 70 mg. per 100 cc. and a PSP excretion of only 3.5% in 15 minutes when she was first seen.

The case history of one patient in whom there has been a good result after 18 months of therapy is as follows:

Case Report. P.G. #40–00–24, a 36-year-old white housewife was admitted with the complaints of headache, fatigue, dyspnea, orthopnea, and swollen ankles for one year. The headaches had become more severe, and her vision blurred in the last 3 months before admission. Eleven years before she had albuminuria during her first pregnancy; and generalized edema, hypertension, and albuminuria during her second (and last) pregnancy 6 years previously.

Physical examination showed a hypertension ranging from 190/110 to 240/140, but usually about 220/120. There were 3 to 4 diopters of papilledema bilaterally. With sodium amytal, the blood pressure fell to a low of 150/110. Moderate cardiomegaly was present.

Laboratory findings included the following: The specific gravity of a random urine sample was 1.027. The NPN was 32 mg. per 100 cc. A PSP test showed 10% excretion of the dye in 15 min., and 55% in 2 hours.

Hexamethonium therapy was instituted in the hospital and a marked blood pressure reduction was obtained. However, after 10 months of oral hexamethonium therapy the patient stopped the medication due to frequent syncopal episodes, nausea, and vomiting. The papilledema which had disappeared after 3 months of therapy recurred, together with dyspnea and dependent edema. A diastolic gallop rhythm was also heard. The blood pressure was recorded in the outpatient clinic as 256/168 recumbent, 240/156 sitting, and 240/156 standing. After digitalization she improved moderately. She remained very sensitive to small doses of hexamethonium parenterally, and reserpine was begun, 0.5 mg. at bedtime. Six weeks later her blood pressure was 188/94 recumbent, 166/98 sitting, and 166/104 standing. She felt sleepy most of the time and complained of a very "stuffy" nose. Since her systolic pressure was below 170 mm. of mercury, sitting (at home) she stopped taking hexamethonium. After 10 weeks of reserpine therapy the optic discs appeared well marginated and there were no retinal hemorrhages or exudates. The patient was up and about doing her own housework and looking for a job. The blood pressures last obtained in the outpatient clinic were 180/118 recumbent, 180/116 sitting, and 158/106 standing.

GROUP IV. Patients who have previously been treated by sympathectomy and still maintain hypertension constitute a special problem. A group of 12

such patients were collected from the surgical oupatient clinic.* All of these patients were hypertensive even in the standing position.

The result of therapy in this group of patients is presented in Table 4. Only 3 of the patients are presently taking hexamethonium, all parenterally. These three have achieved a considerable reduction in their blood pressure. Two of them, in congestive heart failure and with severe headache are now working daily. The third patient, with a strong family history of migraine, still has severe headaches.

TABLE 4.—POST-SYMPATHECTOMY PATIENTS

Number of Patients	12
Age (in years)	
Average	42
Range	28 to 57
Duration of therapy (in months)	
Average	21
Range	2 to 37
Sex	
Male	4
Female	8
White	10
Colored	2

AVERAGE BLOOD PRESSURE IN MM. OF MERCURY

	Before Treatment	*After Treatment*
Recumbent	212 ±† 21	200 ± 33
	129 ± 11	118 ± 15
Sitting	204 ± 10	183 ± 27
	130 ± 8	117 ± 9
Standing	196 ± 18	171 ± 28
	132 ± 7	113 ± 12

AVERAGE BLOOD PRESSURE CHANGES IN MM. OF MERCURY

	Number of Patients		
	Recumbent	*Sitting*	*Standing*
Systolic ↓ 20	6	9	5
Systolic ↑ 20	1	0	0
Diastolic ↓ 15	6	6	6
Diastolic ↑ 15	0	0	0

†± Refers to one standard deviation.

Discussion. A major problem in the evaluation of therapy remains the comparison of similar groups of patients. The difference in the disease between male and female, and colored and white patients has been commented upon by many authorities[1,5,11,14]. In general, women withstand their hypertension better than men, and the disease is more severe in the Negro.

Various means have been used by different investigators in their efforts to evaluate the result of therapy in hypertensive vascular disease. Smithwick[14] stated that the mortality rates are the only really valid method. Such a method requires many patients and a prolonged period of study. Most reports, however, deal with comparisons of the blood pressure before and after therapy, and usually for short periods of time.

Many of the problems involved in using the blood pressure as an index of therapeutic effect can be summed up by the following questions: What is the base line blood pressure? What should be considered the final blood pressure under treatment? What is a clinically significant reduction of the blood pressure? The marked variation in the blood pressure in any given patient makes an absolute answer to the first 2 questions impossible unless repeated 24-hour mean blood pressure records were available both before and after therapy. Likewise, it is difficult to arrive at the amount of reduction

*These patients and their records were made available through the courtesy of Dr. Geza DeTakats of the Department of Surgery, College of Medicine, University of Illinois and the Research and Educational Hospitals. Dr. DeTakats comments "The causes of failure to achieve a lowering of diastolic pressure by surgical treatment have not been investigated in this study and are frequently unclear."

of the blood pressure which would be clinically significant. Some observers have used a reduction of 20 mm. of mercury systolic, and 15 mm. of mercury diastolic as there index of significance. In addition, there is still discussion as to the value, or even advisability, of reducing the blood pressure in hypertensive patients.

We have used the blood pressure as a means of evaluating response to therapy, but with recognition of the serious limitations inherent in this exceedingly variable measurement. The records of blood pressures taken by the patients themselves in their homes (those treated with hexamethonium) have not been used. Home blood pressures are usually lower than those obtained by the physician. In one of our patients, the difference between the patient's own recording at home and the value obtained by the patient and ourselves in the outpatient clinic was 90 mm. of mercury (systolic). The comparison of home values of the blood pressure, with base line values obtained in the outpatient clinic or hospital would thus yield falsely encouraging results.

When hexamethonium, or any agent producing postural hypotension, is employed, the position in which the blood pressure is recorded and the length of time after the last dose of the drug become important factors[8]. We have not attempted to control the time interval but have noted that most of our recordings of the blood pressure took place approximately 3 hours after the last dose of hexamethonium. That such matters mentioned above must be carefully considered in any contribution on the subject of therapy of hypertensive vascular disease is attested to by the meteoric rise and fall of enthusiasm for each new drug advocated in recent years.

No conclusions can be reached with the small groups of patients, described here, but together with the reports of others, we have arrived at certain impressions. Wilkins[15] has pointed out that the single alkaloid, reserpine, seems to embody all of the desirable actions of *Rauwolfia serpentina*. The ideal patient (one in whom the drug could be expected to be effective) is said to be relatively young, with a labile hypertension, diastolic pressure below 120 mm. of mercury, and a tachycardia. Some patients who seem to fit these criteria do not respond (10 of our 26 patients). On the other hand, one of our patients with severe disease and papilledema did respond. The effect is slow to appear and disappear, and consists of mild to moderate reduction in the blood pressure, sleepiness, increased appetite and weight gain, and bradycardia. *Rauwolfia serpentina* counteracts the tachycardia produced by hydralazine, and aids some patients in controlling the constipation due to hexamethonium. *Rauwolfia serpentina* would seem to be the best drug now available, to try first in ambulatory patients with hypertensive vascular disease.

Hexamethonium, or other ganglion blocking agents, should be used only in patients with severe hypertensive vascular disease and is begun in the hospital. The patient must be reasonably intelligent and cooperative, for he must be taught to take his own blood pressure, and to adjust the dose of hexamethonium accordingly. The chronic use of hexamethonium carries a definite risk of recurrent syncopal episodes, while its parenteral use has the obvious inconvenience of repeated injections albeit fewer episodes of syncope. By either route of administration, constipation, dry mouth, and blurred vision are almost universal complaints. Hexamethonium is particularly difficult to use in patients previously treated by

sympathectomy due to increased sensitivity to postural changes which leads to syncopal episodes. Parenteral rather than oral hexamethonium partially solved this problem through a finer adjustment of dosage than is possible with oral hexamethonium. In any case, a compromise must be made and the dose adjusted to obtain the greatest reduction in blood pressure without severe postural hypotension. Smithwick[14] has pointed out that evaluation of therapy is particularly difficult in patients treated by sympathectomy. Only 45% of his operated patients maintained a reduction in blood pressure for 5 years, but their mortality rate remained lower than in the group he used as a control.

Several patients previously sympathectomized had a very high blood pressure, but had few symptoms or findings. In such patients hexamethonium is not now used. When its use was attempted in several patients, they soon stopped taking the drug because of the symptoms which it induced. As a result these patients now take hydralazine or *Rauwolfia serpentina*, or both; or no medication at all.

Hexamethonium must be used with particular caution in the face of renal insufficiency because it is excreted unchanged by the kidneys[6]. Renal insufficiency, in general, is the most definite limiting factor in the therapy of hypertensive vascular disease, and results in its presence, regardless of the therapy used, are poor. Hexamethonium is also useful in the control of congestive heart failure due to hypertensive cardiovascular disease[7], and occasional patients may be able to discontinue the use of digitalis. Hydralazine, or *Rauwolfia serpentina*, or both, when given with hexamethonium may produce a greater reduction in the blood pressure (or reduce the amount of hexamethonium needed) and may decrease the severity of the undesirable side effects.

The best results of therapy are in the white females with only slight elevation of the NPN, in some of whom it may be possible to reverse the "malignant" process. It is interesting to note that in this group of 66 patients, 7 of the 10 deaths occurred in Negro males.

Summary. 1. The serious limitations in the use of the blood pressure response in the evaluation of therapy of hypertensive vascular disease have been stressed.

2. Of 26 patients with benign hypertensive vascular disease treated with *Rauwolfia serpentina* alone for an average of 10.5 months, 14 achieved a reduction in diastolic pressure of 15 mm. of mercury or more.

3. Nineteen patients with severe hypertensive vascular disease, treated with hexamethonium, hydralazine, and *Rauwolfia serpentina* for an average of 14 months have achieved an average reduction in blood pressure (standing) of 45 mm. of mercury systolic, and 25 mm. of mercury diastolic.

4. Thirteen patients with "malignant" hypertension were treated with hexamethonium, hydralazine, and *Rauwolfia serpentina*. Of the 6 patients still living, 5 are white females who had a near normal NPN initially. All 4 Negro males in this group died.

5. Hexamethonium has proven difficult to use in 12 post-sympathectomy patients due to repeated episodes of syncope.

6. In 66 patients of all types, there have been 10 deaths, of which 7 were in Negro males.

7. While therapy is drastic in many of the patients, and reduction of blood pressure worsened the clinical well-being of some patients, certain dramatic improvements were obtained, including the reversal of papilledema.

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A NEW APPROACH TO THE TREATMENT OF GASTROINTESTINAL DISTRESS

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The frequent occurrence of disturbed digestive function in executives, creative workers and others whose occupations subject them to mental and emotional stress is well known. Studies[1,10,13] have demonstrated that the repeated appearance of gastrointestinal malfunction in people with demanding, responsible positions, poses a serious problem to industry and medicine.

Other writers[2,4,11,15,16] have pointed out that the emotional problems of the visceroneurotic, "the man who lives in his gut," may result in pathologic change. This paper reports on a study of 76 patients which may indicate a therapy of value for treating the mental and physical symptoms of gastrointestinal distress.

THE "TYPICAL" PATIENT. The classic victim of psychogenic gastrointestinal disorders is almost always described as a harried, pressure-laden executive who frequently exhibits what Harms and Soniat[8] have described as the "Business Man's Syndrome": a personality pattern characterized by a deep seated feeling of inadequacy and subsequent over-compensation resulting in a compulsive, often frustrating drive for success. There is no doubt that most visceroneurotics fit nicely into this category; yet it is also true that a good many others do not. In this study two patients who have the mental-emotional symptoms characteristic of the "Business Man's Syndrome" are 14-year-old schoolgirls. Dr. Bertram Girdaney[6] has reported that in his pediatric practice he treats about 43 peptic ulcer patients a year, all of whom demonstrate the tension and anxiety which accompany this condition. Their ages range from 14 months to 11 years.

RATIONALE. Emotional stimuli are thought to be responsible for the origin and recurrence of pathogenic gastrointestinal disorders; they are clearly the cause of the less well defined "functional" disturbances. If we neglect the treatment of these emotional factors we may hinder the patient's physical recovery; for even if the pathological condition is organic in origin, it may be accompanied by fears and anxieties which must be alleviated before therapy can be wholly effective. Although psychotherapy often provides the ultimate answer to many of the visceroneurotic's problems, the practicing physician must frequently supply an immediate treatment for the patient's complaints.

Previous studies[3,7,14] have suggested the use of a d-amphetamine-amobarbital combination* for the relief of nervous tension and anxiety. The author's experience with this compound suggested that it, in conjunction with belladonna, might result in an effective treatment for gastrointestinal distress. Sidney Portis[12] demonstrates that the digestive tract is probably the seat of altered emotional response because of its abundant afferent and efferent nerve supply and the ease of transmission of emotional stimuli from the hypothalamus region to the digestive

*Dexamyl, Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

organ. Reports[5,9] suggesting that d-amphetamine sulfate acts on the hypothalamus gave an added indication for the use of this drug.

Method and Material. Dexamyl plus belladonna was given to 76 patients who had suffered from digestive disturbances, either constantly or intermittently, for from 1 to 20 years. Most had a history of recurrent signs and symptoms and recognized the connection of these with tension. All were thoroughly studied, and had complete gastrointestinal roentgenograms. Some patients presented organic lesions, but most conditions were eventually defined as "functional."

SELECTION OF PATIENTS. No attempt was made to select patients of a certain type. The patients represent "run of the mill" cases that appear in the physician's office. Although the majority were people in positions of economic responsibility, a good many (25%) were not. This latter group was composed of 2 schoolgirls, 6 widows, 8 married women and one retired male. The diagnoses were varied (Table 1). A great majority of these patients (70%) had been previously treated by many different methods without experiencing any beneficial effect.

TABLE 1.—LIST OF DIAGNOSES

	Number of Patients	*Age Range*	*Sex*
"Functional"	51	14–72	13 males 38 females
Duodenal ulcer (all ulcers were recurrent)	13	30–72	11 males 2 females
Post-cholecystectomy	9	43–70	4 males 5 females
Resection of bowel for carcinoma	2	49–61	2 females
Carcinoma of stomach	1	87	1 female

DOSE. The d-amphetamine sulfate (5 mg.), amobarbital (32 mg.) combination plus belladonna (0.2 mg.) was administered to 76 patients over periods ranging from 4 weeks to 6 months. The dosage was determined by the age, sex and physical condition of the patients. Those whose roentgenograms showed the presence of duodenal ulcer received 1 or ½ dose every 3 hours or 1 dose and ½ dose alternately every 3 hours. A few received ½ dose every 3 hours. Other patients who did not have ulcers, but who had other symptoms (indigestion, diarrhea, and the like) received 1 dose t.i.d. either before or with meals, with an occasional additional dose between lunch and supper.

The original dose given to 10 patients at the beginning of the study consisted of 32 mg. of amobarbital and 0.4 mg. of belladonna. Four of the 10 patients complained of blurred vision; consequently, the belladonna dose was reduced to 0.2 mg.

Results. Two patients discontinued the treatment in the first 48 hours: One developed urticaria; the other complained that she "didn't feel any better" and refused to take further medication.

The therapy was successful in all 74 of the remaining patients. The belladonna contributed the desired antispasmodic effect, and the mood action of the Dexamyl resulted in the alleviation of tension and anxiety. All patients felt more cheerful and relaxed. The "fussy" attitude these people took toward eating changed considerably, and many of them gave up odd dietary habits to return to sensible foods. All patients were able to eat a wider variety of foods without experiencing ill effects.

The treatment had an interesting effect on weight. Ten patients who where underweight gained an average of 5 pounds during treatment, and 8 patients who were overweight lost an average of 15 pounds.

SIDE EFFECTS. Except for the urticaria experienced by one patient, there were no undesirable side effects.

Case Reports. Three of the 4 following case histories are illustrative of the majority of patients treated in the study. The fourth history reports on a more uncommon use of the drug; one which may be deserving of some attention from other investigators.

CASE 1. A depressed, nervous, 42-year-old male with a tendency toward alcoholism (his alcohol intake had varied from 10 to 20 ounces daily for the past 6 years) was treated for a perforated duodenal ulcer. A satisfactory repair was performed, and a roentgenogram taken a month later showed excellent function, hyperperistalsis and some pylorospasm. The free gastric hydrochloric acid was elevated. While in the hospital the patient was treated with antacids and rather heavy doses of barbiturates and codeine. He complained that although the combination of barbiturates and antacids had partially relieved his epigastric distress, he still suffered a good bit of pain and was quite depressed. He had not been drinking since the operation. Dexamyl plus belladonna (one dose every 4 hours) was substituted for the barbiturate-codeine combination; he discontinued the medication in 4 months, but later reported that when under tension he occasionally used a half strength dose. He is much more cheerful and relaxed, and has not returned to the use of alcohol.

CASE 2. An excitable, tense, 43-year-old male had a recurrence of duodenal ulcer after being symptom-free for 19 years. Treatment with barbiturates and antacids did not give satisfactory results; consequently, the barbiturates were withdrawn and Dexamyl plus belladonna (one dose every 4 hours) was given in addition to antacids. He reported complete symptomatic relief and a definite diminution of tension. The treatment was continued for 3 months. When last seen he had no complaints, and there was no evidence of relapse.

CASE 3. A 55-year-old engineer had a third recurrence of duodenal ulcer; prolonged self treatment with antacids gave him no relief. This patient had previously received belladonna and barbiturates but had found the medication depressing and was hesitant about taking any similar preparation. He was given Dexamyl plus belladonna (1 dose every 3 hours) with excellent results. He continued the medication for 3 months; roentgenograms taken at that time were negative for ulcer. There has been no recurrence.

CASE 4. An 87-year-old woman's roentgenograms revealed a "large neoplasm of the lesser curvature." Because of the size of the growth and the patient's advanced age and poor circulation, a surgical consultant advised against resection. The patient complained of severe abdominal pain and was anxious, irascible and pessimistic. She was placed on sedatives at night and was given Dexamyl plus belladonna (1 dose every 3 hours). During the next 8 months she did remarkably well. Her symptoms were almost completely relieved, her anxiety was much less marked, and her outlook on life was serene and optimistic. She was then confined to bed and opiates were occasionally needed. She died of her disease one month later. The Dexamyl-belladonna combination, by producing an amelioration of her symptoms and an excellent mental attitude, contributed a great deal to this patient's happiness in the last year of her life.

Discussion. The results of this study suggest that the emotional stress which may cause and usually accompanies gastrointestinal disorders is beneficially affected by the d-amphetamine sulfate-amobarbital combination. Although no drug therapy can give the final answer to mental-emotional problems, the mood alleviating action of the compound provides relief from psychic symptoms which greatly enhances the possibility of physical recovery. The belladonna, because of its antispasmodic action, is a valuable adjunct to this therapy. The success of this combined therapy in providing relief of pain and elevation of mood in the patient suffering from an inoperable cancer suggests that Dexamyl plus belladonna may be of value in the supportive treatment of patients afflicted with an incurable disease.

It would seem, then that the use of d-amphetamine sulfate-amobarbital combination plus belladonna provides a useful, easily administered therapy for the treatment of gastrointestinal distress.

Summary and Conclusion. 1. Treatment with a d-amphetamine sulfate-amobarbital compound for the alleviation of psychic stress and belladonna

for physical relief was tried on 76 patients who had suffered from digestive disturbances for from 1 to 20 years. Most of these disturbances were defined as "functional."

2. Two patients were not helped by the treatment; 74 were. The d-amphetamine-amobarbital combination relieved the nervous tension and anxiety found in these patients, and the belladonna had a desirable antispasmodic effect. All patients became more relaxed and cheerful, and were able to eat a wider variety of foods without ill effect. Eight patients who were overweight lost an average of 15 pounds. Ten who were underweight gained an average of 5 pounds.

3. It was suggested that the success of the combination in the supportive treatment of an elderly woman suffering from an incurable, inoperable cancer might indicate another use for the medication.

4. It was concluded that the d-amphetamine sulfate-amobarbital combination plus belladonna provides an effective, easily administered treatment for the symptoms of gastrointestinal disorders.

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THE NEUROLOGICAL MANIFESTATIONS OF CAT SCRATCH DISEASE

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Neurological manifestations of cat scratch disease have been recognized since 1952, when the first report of encephalitis associated with this entity was published[14]. There have since been a total of 9 recorded cases in which neurological syndromes have been noted. The purpose of this paper is to present an additional instance of cat scratch disease in which severe nervous system involvement, meningomyeloencephalitis, occurred and to classify the findings in the previously reported patients.

Since 1932, when Debre[4] and Foshay[7] independently recognized cat scratch disease as a clinical entity belonging to the group of benign reticuloendothelioses, and following the publication of the first report of this disease in the United States by Greer and Keefer in 1951[9], nearly 200 cases have been described from various parts of the world. Although in the majority of instances the clinical changes have been associated with and limited to the lymphatic system, Daniels[3], Usteri and his co-workers[16], Debre[5], Adams *et al.*[1], and Belber, Davis and Epstein[2] have recorded the appearance of skin lesions resembling erythema nodosum, pulmonary infiltration, surgically proved mesenteric lymphadenitis, an osteolytic lesion of the mandible and thrombocytopenic purpura. In each of these patients, the diagnosis of cat scratch fever was made on the basis of a positive skin test alone or in conjunction with biopsy study of an involved node, or by means of a rising titer of complement fixing antibody. The affected lymph nodes exhibit microabscesses, reticuloendothelial hyperplasia, lymphocytic cuffing of blood vessels and giant cells[1,8].

In addition to the above-mentioned lesions which have been observed outside of the lymph nodes, involvement of various parts of the nervous system has also been noted. Instances of encephalitis, myelitis and radiculitis, and encephalomyelitis have been recorded by Stevens[14], Debre[5], Thompson[15], Daniels[3], Usteri *et al.*[16], Grossiord[10], Depaillat[6], and Roget[13]. The case described below illustrates the extent and severity of the neurologic disorders which rarely complicate cat scratch disease.

Case Report. The patient was a 17-year-old white married girl who entered the hospital with a tentative diagnosis of poliomyelitis because of signs of meningeal irritation and weakness of the legs. It had been her custom for some time to allow a pet cat to sit on her abdomen while she lay in bed; as a result, she had suffered numerous scratches

in this area. Seven days before admission, she was scratched deeply on the dorsum of the right hand by her cat. Bleeding occurred but was of small quantity. Not until 4 days later were there any symptoms of infection. At this time a severe throbbing headache, a temperature of 102° F., and nausea and vomiting appeared. Diarrhea and severe back pain were also present. Pain and tenderness over the right breast and in the right axilla, aggravated by a tight brassiere, were noted at the same time. The following day, the neck and back became stiff. The family physician prescribed tetracycline and salicylates. By the next morning, all of the symptoms ameliorated but as the day progressed, the stiffness became so marked that movement was difficult. On the following day, because of the development of weakness of both legs and loss of sensation extending to the hips, the patient was admitted to the Haynes Memorial Hospital.

Physical examination revealed an apathetic, drowsy, pallid young woman who spoke in a barely audible voice; she frequently ignored questions completely and appeared to evade others by oblique answers. She was well oriented as to time, space and person. She complained of pain in the back. The temperature was 99° F., the pulse 70 and respirations 20 per minute. Blood pressure was 120/60. There were small, nontender cervical, axillary and inguinal nodes. The neck was stiff and the back was rigid. Examination of the heart, lungs and abdomen revealed no abnormalities. Axillary hair was absent. Four deep, red and crusted wounds 5 to 8 cm. in length were present on the dorsum of the right hand. The skin immediately adjacent to the lesions was moderately reddened and edematous.

Neurological examination revealed the following: The neck and back were stiff and the Kernig sign was positive. Gag reflex was absent but the corneal reflex was intact. No other cranial nerve defects were noted. All of the deep and superficial reflexes were present, normal in strength and equal on both sides of the body. Both plantar responses were at first flexor, but after 2 days, an extensor reaction was elicited on the left. Perception of pain, touch and temperature was absent in both feet and lower legs and greatly diminished as high as the iliac rests anteriorly and the level of the 10th thoracic vertebra posteriorly. All sensation was preserved in a small area over the sacrum. Vibratory sense was absent from the toes to the level of the clavicle on the left and the lower costal margin on the right. Position sense was lost in both lower extremities but present in the upper ones. The muscles of the arm and trunk were of normal strength. Marked weakness and spasticity of all of the muscles of the legs, from the hips to the toes, were striking.

Examination of the urine revealed no abnormalities. The hemoglobin was 14.4 gm. per 100 cc. and the hematocrit 44%. There were 7250 white blood cells per c.mm. of which 64% were neutrophils, 34% lymphocytes and 1% each monocytes and eosinophils. The pressure of the spinal fluid was normal. It contained 916 cells per c.mm., 99% being lymphocytes and 1% neutrophils. The protein content was 150 mg. and the sugar 90 mg. per 100 cc. The colloidal gold curve was 1112210000, and the culture revealed no organisms. Study of the cerebrospinal fluid 4 days after admission revealed 122 cells per c.mm., all of them lymphocytes, 103 mg. protein and 71 mg. sugar per 100 cc. The number of cells in the spinal fluid was reduced to 82 per c.mm. two days later; protein and sugar at this time were 71 and 48 mg. per 100 cc., respectively.

Because of pain in the back and stiffness of the neck, hot packs were applied and various analgesics administered; only moderate relief of the distress was produced. For the first several weeks, there was no change in the neurologic findings. The temperature did not rise above 99° F, except on the fifth hospital day when it reached 102° F., but quickly decreased to normal. The patient complained frequently of pains in various areas, especially in the abdomen; in no instance, however, was there fever, leukocytosis or any demonstrable physical abnormalities which could be associated with the symptoms. Physiotherapy was started after the first few days in the hospital. The patient cooperated poorly with this treatment. She exhibited severe emotional upsets interspersed with periods of anorexia which were so severe and prolonged that she was fed by gavage for many days. In the 16 weeks which she spent in the hospital, the emotional difficulties gradually disappeared and the motor and sensory defects improved so that at the time of discharge, the patient was able to walk with no assistance and exhibited only minor sensory defects.

Studies carried out with acute and convalescent phase serums revealed no antibodies for infectious mononucleosis, herpes simplex, lymphocytic choriomeningitis, or Brucella. The Frei and lygranum complement fixation

tests were negative. Endermal injection of 0.1 cc. of cat scratch antigen produced, at the end of 24 hours, a papule (0.5 cm. in diameter) surrounded by a zone of erythema (about 3 cm. in diameter). The test was repeated in another site several days later and gave a reaction of the same type and intensity as the first one. The patient's husband who had never been scratched by the cat was also given an endermal injection of the same antigen; he showed no reaction.

Discussion. The diagnosis of encephalomyelitis due to cat scratch disease in the patient described above was made on the basis of (1) a history of a wound produced by a cat, (2) axillary and sub-pectoral pain and tenderness, (3) evidence of an inflammatory reaction at the site of the scratches, (4) a positive endermal reaction with cat scratch antigen with a negative test in a family control and (5) the development, about one week after injury, of a clinical picture characterized by an abnormal spinal fluid, sensory and motor losses and marked emotional disturbances. The positive skin test alone is insufficient ground on which to base a diagnosis of cat scratch disease because this reaction may remain positive for a long period of time after the acute process has subsided. In this case, this finding was considered only as additional evidence for cat scratch disease as the cause of the encephalomyelitis. Most emphasis was placed on the history of injury by a cat and the subsequent development of an inflammatory reaction at the wound site as well as lymphadenitis. Although axillary lymphadenopathy was no longer apparent when the patient entered the hospital, the symptoms which occurred 4 days after wounding are entirely consistent with those which have been recorded in instances of uncomplicated cat scratch disease.

A review of the 9 cases of "encephalitis" which have been reported in association with cat scratch disease reveals 3 different syndromes. Manifestations of encephalitis alone, of myelitis and radiculitis alone, or of encephalomyelitis may occur. The pertinent laboratory and clinical findings in the 9 previously described patients as well as the one recorded in this paper are presented in Table 1.

Seven of the cases described in Table 1 can be classified as instances of encephalitis[3,5,6,13-16]. The oldest individual in this group was 16 and the youngest 4 years old; the average age was 11. The time interval between the onset of cat scratch disease and the development of signs of nervous system involvement was 3 to 20 days in most of the patients; in one the "latent" period was 5½ weeks. The onset of the encephalitis was abrupt, the temperature reaching 104 to 105° F. in a few hours. Despite the high fever, coma and convulsions, the white blood count was usually normal. The spinal fluid was abnormal in only 2 cases. Transient neurologic changes were noted in several cases at the height of the fever. In one person, there was weakness of the right arm and a facial palsy of the central type which disappeared rapidly; in one, respiratory depression and apnea requiring the use of a mechanical respirator, occurred; several others exhibited transient paralysis of the ocular muscles or extensor plantar responses. Defervescence was usually rapid and all manifestations disappeared in 48 to 72 hours. In general, residua were few and nonspecific in character. One child had a limp which persisted for several weeks, while several patients were considered to be abnormally irritable. In 2 instances, convulsions and fever recurred, but lasted for only a very short time. Four cases were studied with the electroencephelogram; 3 exhibited nonspecific changes of brief duration.

TABLE 1.—REPORTED CASES OF "ENCEPHALITIS" IN CAT SCRATCH DISEASE

Authors	Stevens[14]	Debre[5]	Debre[5]	Thompson[15]	Usteri *et al.*[16]	Grossiord[10]	Depaillat[6]	Roget[12]	Daniels[3]	Weinstein and Meade
Age	13	4	48	16	35	21	13	13	8	17
Location	United States	France	France	United States	Switzerland	France	France	France	United States	United States
Sex	Male	Female	Female	Male	Female	Male	Female	Male	Female	Female
Source of infection	Unknown	Cat-presumed	Cat scratch	Brush burn—cement floor	Probable cat	Unknown	Not known	Not known	Cat	Cat
Method of diagnosis	Skin test Complement fixation	Skin test	Skin test	Skin test	Skin test	Skin test	Complement fixation Skin test	Skin test	Skin test	Skin test
Spinal fluid	Normal twice	18 cells, 75 mg. prot. 11 cells, 20 mg. prot.	8 cells, 50 mg. prot. 3 cells, 20 mg. prot.	Normal on two occasions	82 cells, 43 mg. prot.	16 cells, 45 mg. prot. 3 cells, 40 mg. prot.	Normal	1 cell, 25 mg. prot. 3 cells, 40 mg. prot.	Norma	916 cells, 150 mg. prot. 122 cells, 106 mg. prot. 82 cells, 72 mg. prot.
Affected lymph nodes	Right axillary	Left submaxillary	Epitrochlear, axillary	Right axillary	No adenopathy	Right axillary	Left inguinal	Inguinal	Right axillary	Probable right axillary and subpectoral
Interval between onset of primary disease and appearance of CNS manifestations	More than one week	Not stated	Three days	Five and one-half weeks	About ten days	Twenty days	Not known	Over eight days	Not known	Seven days
Clinical manifestations	Fever, convulsions, coma, nuchal rigidity. Transient weakness of right arm and central weakness of right facial nerve. Positive Babinski. Cleared in three days	Fever, convulsions, coma and transient respiratory failure. Onset after fever was declining. No mention of nuchal rigidity or of Babinski. Cleared in two days	Transient fever. Myoclonic twitching. Weakness left arm. Decreased reflexes. Severe upper arm pain. Myosis, left. Sensory changes. Slow recovery in four months	Fever, coma, nuchal rigidity, diminished reflexes in knees and right arm. Babinski +. Transient. Recovery in forty-eight hours. Reflexes normal.	Fever, stiff neck and back. Headache, Babinski present	Fever. Weakness of all extremities. Reduction in reflexes. Urinary retention. Loss of sensation in lower legs. Stupor. Difficulty in breathing. Afebrile in two days	Fever, coma, convulsion Defervescence in a period of two days	Fever, coma, convulsion. Delusions. Complete recovery followed by recurrence of syndrome in eight days. Rapid defervescence with no residual changes	Fever, coma, convulsion. Stiff neck and bilateral Babinski Symptoms cleared in two days, although nodes later went on to suppurate	Fever, nuchal rigidity. Apathy. Spasticity and weakness of legs. Babinski + on left. Marked pain, touch, temperatures. Vibratory sense loss. Severe emotional disturbances. Fever absent at time of admission
Sequelæ	Tended to drag leg. Was irritable	Single recurrence of convulsions, several days later EEG abnormal	None, but patient had a history of chorea and von Economo's encephalitis	Irritability was only sign after diseases faded.	Apathy remained for several weeks	Bladder still weak after four months	None save abnormal EEG	Abnormal EEG	Normal EEG	Patient had weakness and sensory changes for at least six months after admission to hospital

Despite the severity of the initial manifestations, the prognosis for complete recovery of the encephalitis of cat scratch disease appears to be excellent; long-term follow-up studies have not yet been carried out, however.

One of the patients[3] described in Table 1 developed a syndrome consistent with myelitis and radiculitis, presumably as a complication of cat scratch disease. She was an adult in whom the source of the infection was a cat scratch. Hyporeflexia, abnormal spinal fluid, motor weakness, sensory changes and myoclonic twitching in one extremity characterized the illness. The myoclonic movements are, however, difficult to attribute to the cat scratch disease because the patient had had encephalitis lethargica and Sydenham's chorea in the past. Recovery was rapid and complete. The severe pain in the arm was attributed by Debre[5] to a radiculitis. The diagnosis of cat scratch disease was based on the presence of axillary lymphadenopathy following injury by a cat and a positive skin reaction with the specific antigen.

The patient reported in this paper is an example of severe encephalomyelitis occurring during the course of cat scratch disease. Beginning approximately one week after suffering deep cat scratches on the hand and progressing for some time afterwards, signs of meningeal irritation, weakness and spasticity of the legs with normal reflexes, extensor plantar responses, loss of sensation in the lower extremities, increase in cells and protein in the spinal fluid and severe emotional disturbances developed. The neurologic abnormalities which were present are those which arise when both brain and spinal cord are involved. This case appears, at the moment, therefore, to be the second recorded instance of encephalomyelitis complicating cat scratch disease; the other is the one described by Grossiord[10]. Both patients illustrate the extent, severity and long duration (4 to 6 months) of the neurologic disorders which may occur in this usually benign and self-limited infection.

The mechanism by which nervous system manifestations are produced in cat scratch disease is unknown. This malady is probably of viral origin[11,12]. It is possible, therefore, that the neurologic disorders are the result of invasion of the neural tissues by the causative agent. As can be seen in Table 1, however, one week or more elapsed between the onset of the infection and the appearance of neurologic disease in 6 of the cases. This resembles the natural history of the post-infectious encephalitides which follow rubeola, vaccinia or rubella or the meningomyeloencephalitides which occur after the administration of horse serum or other immunizing agents. The presence of a latent period suggests the possibility of an allergic type of nervous system reaction, a mechanism which has been implicated, on clinical and experimental grounds, in the known post-infectious "encephalitides"; it is worthy of mention that in these, the brain, spinal cord, or peripheral nerves may be involved separately or in various combinations, as they are in the "encephalitis" of cat scratch disease.

Conclusions. 1. A case of severe encephalomyelitis complicating cat scratch disease has been described. The diagnosis was based on the presence of scratch wounds of the hand, a history suggestive of axillary and subpectoral lymphadenopathy, a positive skin reaction with cat scratch antigen, signs of meningeal irritation, an abnormal spinal fluid, marked emotional disturbance, spastic paraplegia, sensory loss and extensor plantar reflexes.

2. Involvement of the nervous system may complicate cat scratch dis-

ease; encephalitis, myelitis and radiculitis, or encephalomyelitis are the syndromes which have been reported.

3. The mechanism of the neurologic disorders which occur in cat scratch disease are unknown; invasion of the nervous system by the "virus" or an allergic reaction may be responsible.

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PHYSICO-CHEMICAL MECHANISMS IN THE PATHOGENESIS OF CERTAIN HEMOLYTIC ANEMIAS

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The association of increased osmotic fragility of erythrocytes with certain of the hemolytic anemias has been recognized for many years[9,16]. The destruction of the red blood cell is apparently dependent upon the disruption of its membrane with subsequent release of the intracellular contents into the surrounding solution.

There are 3 independent factors related to hemolysis: 1) intracellular osmotic pressure, 2) extracellular osmotic pressure, and 3) the tensile strength of the membrane. Hemolysis varies directly with the intracellular osmotic pressure of the red blood cell, indirectly with the extracellular osmotic pressure, and is limited by the tensile strength of the membrane surrounding the red cell:

$$\text{Hemolysis} \sim \frac{\text{Intracellular osmotic pressure}}{\text{Membrane tensile strength} \cdot \text{Extracellular osmotic pressure}}$$

When the cell is placed in hypotonic solution its ionic concentration is diluted through the transfer of water from the relatively dilute bathing solution. This addition of water into the cell increases the total hydrostatic force exerted on the cellular membrane. When the total number of osmotically active particles per unit volume within the cell is in osmotic equilibrium with its environment, the final volume of the cell (V) is expressed in per cent of normal volume (100%) at tonicity T_0

$$V = RW\left(\frac{1}{T} - 1\right) + 100$$

where R equals a constant that corrects actual findings to fit predicted findings, W equals the initial water content in the cell, and T equals the ratio of the freezing point of the bathing solution to that of the plasma (T_1/T_0). Obviously R equals unity for cells behaving as perfect osmometers[13].

The purpose of the following experiments is to measure each of the 3 factors responsible for hemolysis, namely 1) intracellular osmotic pressure, 2) extracellular osmotic pressure, and 3) the tensile strength of the membrane in each type of known hemolytic disease.

Osmotic pressure is a physical property of a solution which may be determined indirectly through measurement of other physical properties, such as freezing point, boiling point, or vapor pressure. All of these properties depend upon the same phenomenon, that is, the affinity of a solvent for the solute[5].

The degree of depression of the freezing point of any aqueous solution below 0° C. measures the number of

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particles in solution. Substances which dissociate into ions increase the osmotic pressure of the solution as the number of particles increases by dissociation. Osmotic activities of various solutions may be expressed in terms of the strength of a solution of sodium chloride which has the equivalent osmotic activity.

Method. Forty cubic centimeters of whole blood were collected in syringes containing 0.2 cc. of 1:1000 heparin solution. Freezing point determinations were made immediately on a 10 cc. aliquot. Twenty to 25 cc. (depending on the hematocrit) of the remaining blood were then centrifugated at 3000 RPM for 30 minutes. The freezing point of the plasma and of the red blood cells was determined individually. Lysis of the cells occurred spontaneously in the first freezing. After determination of freezing points of plasma and of red blood cells, the samples were transferred to individual dialytic membranes. Freezing point depression due to "ghosts" was found to be negligible.

Determinations of freezing points were made using a standard freezing point chamber[15]. Success in obtaining reproducible results was found to be dependent upon slow and even exchange of heat. Supercooling of a moderate degree is essential to the accuracy of freezing point determinations. Upon crystallization a supercooled solvent releases heat, causing a precipitous rise in temperature until the end point, that is, the freezing point, is reached. Severe supercooling precludes adequate exchange of heat before the freezing point is reached.

Constant exchange of heat was obtained by constant agitation of the solution. Slow exchange of heat through an external medium of air was found to be satisfactory. The end point of all determinations was the point at which a secondary drop in temperature began following the initial rise at the time of crystallization. A Beckman thermometer accurate to within .005° C. was used for determining the freezing points.

Dialysis of red blood cells and plasma was performed using an animal membrane permeable to monosaccharides but not to disaccharides (as determined by freezing points of the surrounding aqueous solution). Ten cubic centimeters of cells or plasma were dialyzed against 5000 cc. of distilled water at 3° C. for 48 hours. The dialysate contained all molecules larger than monosaccharides. The non-dialyzable portion was presumed to be a protein solution containing associated ions since the largest single ionic constituent of intracellular electrolyte is protein[4] and since the portion of the electrolyte of the intracellular fluid not closely bound with protein readily passes through this membrane. In determining freezing points of the dialysates, correction was made for dilution which occurred during dialysis; the degree of dilution was determined by volumetric displacement. An attempt was made to keep the final volume as constant as possible in order to eliminate any error due to inconsistent dilution.

The change in volume of the red blood cells under varying osmotic conditions was studied as follows: Samples of erythrocytes separated from plasma by careful centrifugation were mixed in Wintrobe hematocrit tubes with equal volumes of saline solutions of varying concentrations. After allowing the tubes to equilibrate for 30 minutes they were centrifugated at 3,000 RPM for 30 minutes and the change in the volume of the red blood cell column was read directly. In those samples where hemolysis occurred the proportion of hemolyzed cells was determined by measuring the quantity of the hemoglobin in the supernatant, and a correction for this was made in the volume of the remaining intact cells. The hemoglobin level corresponding to 100% hemolysis was determined by equilibrating red blood cells with distilled water. Less than 100% hemolysis was calculated as a fraction of total hemolysis. A proportionate fraction of the hematocrit reading was added to give a corrected hematocrit. All hemoglobin determinations were performed with a standard electrophotometer.

Using the above method it was possible to construct osmotic fragility curves of erythrocytes. The solutions used were not buffered nor was the temperature controlled beyond that of the environment of the laboratory.

NORMAL DAILY OSMOTIC PRESSURE VARIATION OF PLASMA. Studies were undertaken to determine whether daily fluctuation in the plasma osmotic pressure occurred normally. A subject ingested normal quantities of food with each of 3 meals and fasted between meals; the caloric and electrolytic content of the solids eaten was unknown. Water was the only fluid ingested, its quantity being carefully measured. Freezing point determinations were made on 10 cc. of plasma withdrawn during the periods of fasting and immediately (within 15 minutes) following the ingestion of water or food, or both.

DIFFERENTIAL STUDIES. An experiment was undertaken to determine the variation of intracellular osmotic pressure from cell to cell, by means of hemolysis of discrete segments of the erythrocyte population.

A 600 cc. sample of whole blood was withdrawn a few minutes after death from a patient who had had no previous transfusions and who died suddenly during anesthetic induction for cardiac surgery. The sample was

TABLE 1.—FREEZING POINT DEPRESSIONS OF WHOLE BLOOD, PLASMA, AND RED BLOOD CELLS, AND DIALYSATES OF PLASMA AND RED BLOOD CELLS

Type Material Used for dF	*Blood*				*Dialysates*			
	Cells		*Plasma*		*Cells*		*Plasma*	
Results	*dF*	*NaCl*	*dF*	*NaCl*	*dF*	*NaCl*	*dF*	*NaCl*
Normal								
Patient No. 1	.565	.96	.565	.96	.125	.21	.020	< .03
No. 2	.565	.96	.565	.96	.135	.22	.025	< .03
No. 3	QNS	QNS	QNS	QNS	.105	.18	.030	< .03
No. 4	.575	.98	.575	.98	QNS	QNS	.025	< .03
No. 5	.570	.98	.570	.98	.105	.17	.020	< .03
No. 6	.560	.94	.560	.94	.110	.18	.015	< .03
No. 7	.560	.94	.560	.94	.120	.20	.020	< .03
No. 8	.570	.98	.570	.98	.125	.21	.020	< .03
No. 9	.565	.95	.565	.95	.120	.20	.015	< .03
No. 10	.570	.98	.570	.98	.115	.19	.020	< .03
No. 11	.560	.94	.560	.94	.105	.17	.020	< .03
No. 12	.570	.98	.570	.98	.135	.22	.030	< .03
No. 13	.570	.98	.570	.98	.130	.21	.030	< .03
No. 14	.560	.94	.560	.94	.110	.18	.020	< .03
Average	.565	.96	.565	.96	.120	.19		
Congenital Spherocytosis								
Patient No. 1	.565	.95	.565	.95	.185	.32	.025	< .03
No. 2	.570	.98	.570	.98	.170	.28	.020	< .03
No. 3	.570	.98	.570	.98	.190	.32	.020	< .03
Average	.570	.97	.570	.97	.180	.31		
Sickle Cell Anemia								
Patient No. 1	*.500	.83	*.500	.83	.045	.07	.020	< .03
No. 2	*.505	.84	*.505	.84	.045	.07	.030	< .03
No. 3	.595	.99	.595	.99	.085	.12	.030	< .03
No. 4	.580	.98	.580	.98	.060	.08	.040	< .03
No. 5	.590	.99	.590	.99	.090	.13	.030	< .03
Average	.555	.93	.555	.93	.065	.09	.030	< .03
Sickle Cell Trait								
Patient No. 1	.570	.97	.570	.97	.140	.24	.020	< .03
No. 2	.570	.97	.570	.97	.120	.19	.020	< .03
No. 3	.560	.95	.560	.95	.120	.19	.020	< .03
No. 4	.565	.96	.565	.96	.125	.20	.020	< .03
No. 5	.565	.96	.565	.96	.130	.21	.035	< .03
Average	.565	.96	.565	.96	.125	.21	.025	
Acquired Hemolytic Anemia								
Patient No. 1	.570	.98	.570	.98	.130	.21	.020	< .03
No. 2	.565	.97	.565	.97	.125	.21	.025	< .03
No. 3	.565	.97	.565	.97	.120	.20	.020	< .03
Average	.565	.97	.565	.97	.125	.21	.020	

* Patients not in crisis.
dF (Freezing point depressions) given in °C below 0°C.
NaCl given in per cent.

heparinized upon withdrawal. Osmotic fragility was determined and the osmometric activity was measured in the manner described above. The intracellular osmotic pressure of the intact cells remaining at each dilution of saline was determined by measuring the depression of the freezing points of the dialysates of these residual cells. Corrections were made in each sample for the volume changes resulting from swelling of the cells at each dilution and as before, for the increase in volume during dialysis.

evidence of significantly increased mechanical fragility.

Results. SUBJECTS WITHOUT HEMOLYTIC DISEASE. *Osmotic Pressure.* The osmotic pressure of erythrocytes and of plasma was determined on specimens from 14 normal adult subjects after 5 hours of fasting. The results are recorded in Table 1. These reveal that the red blood cell and its environmental

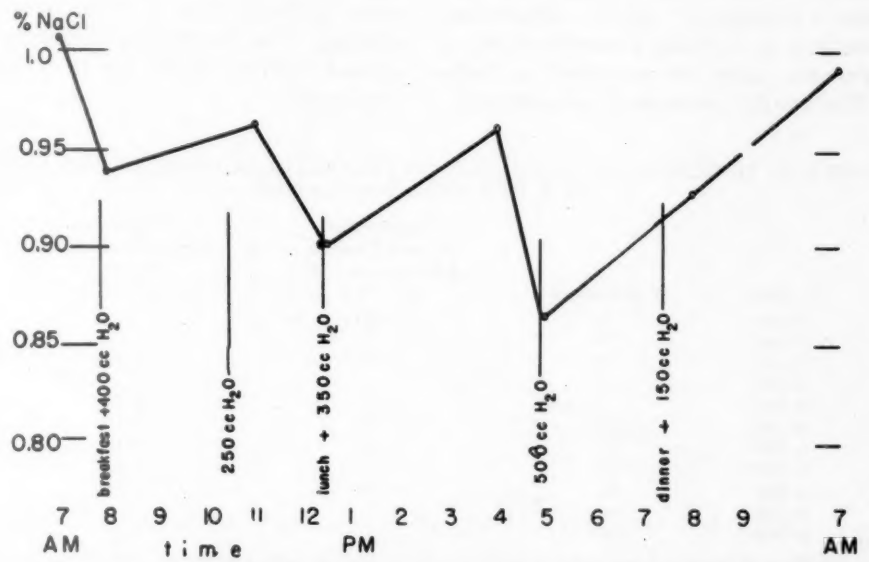

Fig. 1.—Plasma osmotic pressure variation in a normal individual in a 24-hour period. The variation in plasma osmotic pressure is recorded in % NaCl and plotted against a time scale. Vertical figures represent solids and fluids ingested in relation to the sampling periods represented by circles.

MECHANICAL FRAGILITY. The mechanical fragility of erythrocytes was determined by agitation of samples of whole blood in flasks containing glass beads. Each observation was controlled with a sample of normal blood. Only rough qualitative information was thus obtained. The specimens of blood were placed in Erlenmeyer flasks having volumes of 125 cc. and containing 35 glass beads of uniform diameter. They were agitated in a serology rocker for 30 minutes. The blood was then removed, centrifugated and the hemoglobin content of the supernatant was measured. An increase of 1.0 gm.% or more in the level of hemoglobin above the increase seen in a sample of normal blood treated in the same manner at the same time was interpreted as

plasma are in osmotic equilibrium. If one accepts the normal osmotic pressure of isotonic physiologic solutions as equivalent to 0.86% NaCl, the plasma and red blood cells of these fasting subjects are seen to be slightly hypertonic, the mean freezing point corresponding to that of 0.96% NaCl. The range of variation of osmotic pressure in these normal subjects was 0.04% NaCl.

The freezing points of dialysates of red blood cells and of plasma from the 14 normal subjects are recorded in Table 1. The data indicate that the

non-dialyzable protein content of erythrocytes is considerably greater than that of plasma.

Daily Plasma Osmotic Pressure. The range of variation of the plasma osmotic pressure of a normal person during a 24-hour period is recorded in Fig. 1.

Osmotic Fragility and Osmometric Activity. The intracellular osmotic pressures for each segment of cell population remaining after differential hemolysis in varying concentrations of hypotonic saline are recorded in Table 2. The results indicate a consistent decrease in intracellular protein osmotic pressure as the osmotic fragility of the cells decreases.

TABLE 2.—DIFFERENTIAL STUDIES OF INTRACELLULAR OSMOTIC PRESSURES OF A RED CELL POPULATION

% NaCl.	*% Hemolysis*	*Intracellular Osmotic Pressure of Remaining Cells dF (° C.)*	*Calculated Intracellular Osmotic Pressure of Hemolyzed Cells (° C.)*
0.550	0	0.120	
0.525	0		
0.500	1	0.120	0.160
0.475	3		
0.450	5	0.120	0.140
0.425	22	0.110	0.130
0.400	56	0.105	0.120
0.375	82	0.085	0.110
0.350	91	0.080	0.100
0.325	95		
0.300	98		

The left hand column is the %NaCl at which the cells were hemolyzed. The second column represents the % of cells destroyed. The third column indicates the freezing point depression of the dialysates of each residual cell population (the mean of the remaining cells). The last column is a rough calculation of the freezing point depression of the dialysates of those cells hemolyzed at each concentration of NaCl.

STUDIES IN PATIENTS WITH HEMOLYTIC ANEMIA. *Congenital Spherocytosis.* Three patients with congenital spherocytosis were studied. The diagnosis was established by 1) negative Coomb's tests, 2) positive familial history, 3) presence of anemia with bouts of severe hemolytic crisis, 4) positive osmotic fragility tests, and 5) presence of spherocytes in smears of the peripheral blood. The osmotic activities of erythrocytes, of plasma, and of dialysates of erythrocytes and plasma are recorded in Table 1. The data reveal that there is a considerable increase above the normal levels in the osmotic pressure of the intracellular protein; this increase must reflect a high intracellular content of protein. The osmotic fragility curves for patients with congenital hemolytic anemia reveal that hemolysis begins in much higher concentrations of NaCl than it does in normal subjects. The mechanical fragility was normal within limits of the method employed.

Sickle Cell Anemia. The results of osmotic pressure studies in 5 patients with sickle cell anemia are recorded in Table 1. Three patients were in crisis at the time of study. The data from dialysates of red blood cells reveal that the intracellular protein osmotic pressure was below normal in erythrocytes of all of the patients. Patients with sickle cell anemia who were not in crisis had in addition, a significantly lower plasma osmotic pressure. Hemolysis of erythrocytes in patients with sickle cell anemia began in much lower

concentrations of saline than did hemolysis of cells from normal subjects. The mechanical fragility was normal. Osmometric curves of erythrocytes in these patients are displaced to the right of, but parallel to, the osmometric curves of normal cells (Fig. 2). (See Discussion.)

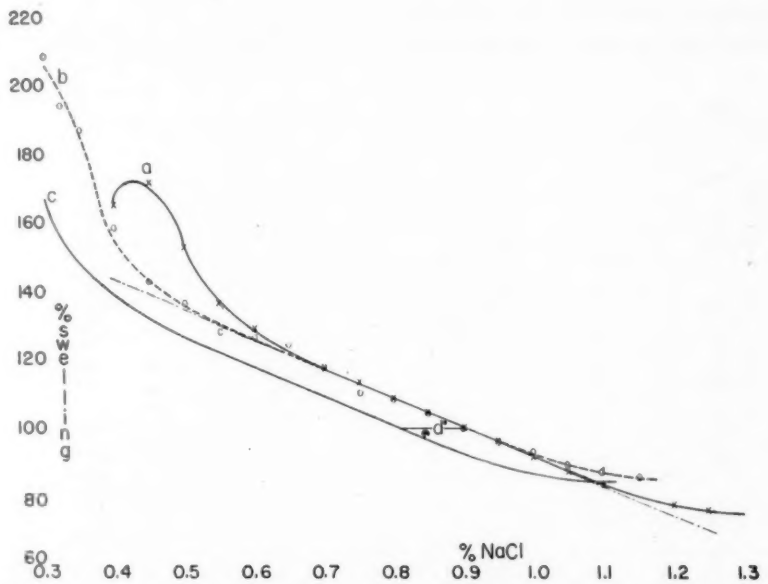

Fig. 2.—Comparison of osmometric activities of normal red blood cells to those of sickle cell anemia. Osmometric activity of the normal red blood cell is represented by line *a*, while the broken line *b* represents the osmometric activity of a sickle cell population. The difference in the points of deviation of the 2 curves from linear osmometric activity (interrupted line) is represented by *d; d* represents the hypotenuse of a right triangle from which *d'* may be calculated (see text). By calculating *d'* for each point on the curve for the red blood cells of sickle cell anemia a resultant curve *c* may be drawn. Curve *c* represents the true osmometric activity of the abnormal red blood cells when compared to normal red blood cells. *d'* also equals the decreased intracellular protein osmotic pressure found in the red blood cells of sickle cell anemia. It will be noted that the sickle cell becomes a normocyte (100% swelling) in 0.78% NaCl.

Sickle Cell Trait. Five patients in whom the sickle cell trait was identified were studied. The osmotic pressures of cells, plasma, and dialysates are recorded in Table 1; the values approximate those of normal persons. Osmotic fragility curves, although appearing to be similar to those of normal patients, had a greater number of cells with decreased fragility. The mechanical fragility and osmometric activity were normal.

Acquired Hemolytic Anemia. The osmotic pressures of 3 patients with acquired hemolytic anemia are recorded in Table 1. The diagnosis was established by the presence of spherocytes in the peripheral smear and a positive Coomb's test with associated anemia. The osmotic activity was within normal limits and the osmotic fragility curves were moderately increased. The mechanical fragility was markedly increased in these patients.

Discussion. Determinations of osmotic pressures of protein solutions

based upon freezing points have been considered as inaccurate[1-3,10-12]. Investigators have introduced formulae for the correction of supercooling or "undercooling"[1,2]. Our experience, however, indicates that adequate heat exchange is critical, and that no matter what the degree of supercooling, results are uniform.

The methods described for osmotic fragility and osmometric activity have here demonstrated do not follow the curve of the perfect osmometer[6,8,13].

A portion of the curve of osmometric activity occurring within the range of daily variation of plasma osmotic pressure may be described by a linear equation:

$$a = \frac{dy}{dx}$$

$$\text{Vol.} = a \cdot \text{Conc.}$$

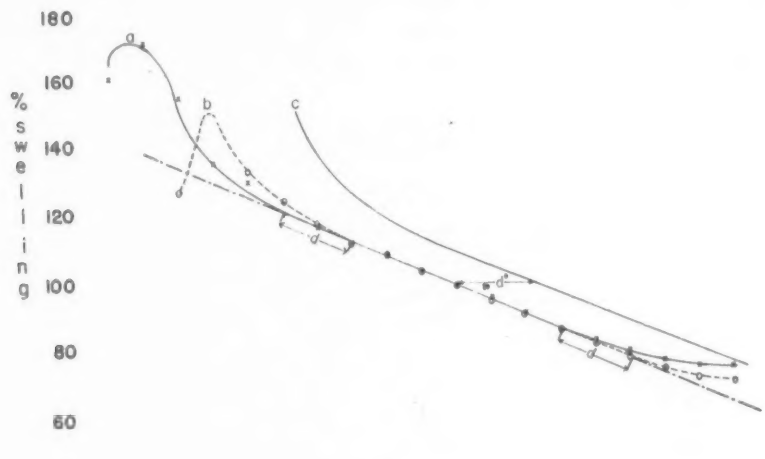

Fig. 3.—Comparison of osmometric activities of normal red blood cells to those of congenital microspherocytosis. Osmometric activity of the normal red blood cell is represented by line *a*, while the broken line *b* represents the osmometric activity of a spherocytic population. The difference in the points of deviation of the 2 curves from linear osmometric activity (interrupted line) is represented by *d; d* represents the hypotenuse of a right triangle from which *d'* may be calculated (see text). By calculating *d'* for each point on the curve for the cells of congenital microspherocytosis, a resultant curve *c* may be drawn. Curve *c* represents the true osmometric activity of the abnormal red blood cells when compared to normal red blood cells. *d'* also equals the increased intracellular protein osmotic pressure found in the red blood cells of congenital microspherocytosis. It will be noted that the microspherocyte becomes a normocyte (100% swelling) in 1.1% NaCl.

several points of error in their techniques. The placing of the cells in equal volumes of hypertonic or hypotonic saline solutions tends to create an error dependent upon a gain or loss of water by the cells. This is borne out by the fact that the osmometric curves

Results recorded in Table 3 indicate an obvious break in the linear relationship at two points above and below isotonicity. These apparent losses of linearity occur at different upper and lower limits, which are constant for each type of abnormal cell studied. A prob-

able explanation for these observations may be found in certain considerations made in the formulation of the equation for the perfect osmometer. It will be recalled that $V = RW\left(\frac{1}{T} - 1\right) + 100$ [13] where V is the volume of the red cell mass at tonicity T, W is the percentage of cell water at normal tonicity (0.9% NaCl), and R is a corrective factor which permits the equation to fit the observed results with the calculated results. The normal cell is assumed to have 70% water ($W = 0.7$) at a normal cell volume of 100% in a solution of 0.9% NaCl. R and W are so related that if an initial assumption as to the water content of the cell is in error, R will be greater or smaller depending on the direction of error in the initial assumption. If R appears to be substantially less than 1.0, the initial cellular water content may be less than 70% at a tonicity of 0.9% NaCl, that is, the cell volume is more contracted at that tonicity than is the volume of a cell for which R is 1.0.

The volume of the water in the red blood cell is, of course, dependent upon its intracellular osmotic pressure. If there is an increase or decrease in the nondiffusable (or colloidal) fraction of the intracellular osmotic pressure, there should be an expected increase or decrease in the total water present in each cell. The change in the water content of the intracellular space will be proportional to the change in the osmotic pressure within the cell, that is, the osmotic pressure of the intracellular protein. It becomes apparent that changes in osmometric ac-

TABLE 3.—THE OSMOMETRIC ACTIVITIES OF THE RED BLOOD CELLS FROM 4 NORMAL PATIENTS, 3 WITH SPHEROCYTOSIS, AND 4 WITH SICKLE CELL ANEMIA ARE RECORDED.

% NaCl.	*Normal Patients*				*Spherocytosis*			*Sickle Cell Anemia*			
	1	2	3	4	1	2	3	1	2	3	4
1.3			75		71	75					
1.25	78	77	76	79	73	76	71				
1.20	80	79	78	81	77	78	73		84		
1.15	82	83		83	79	80	79	87	86	85	85
1.10	86	85	83	85	84	85	84	89	88	87	87
1.05	89	87	87	88	88	88	87	92	90	90	89
1.00	92	91	92	92	92	91	92	93	92	93	92
0.95	96	95	96	96	97	96	96	96	95	96	96
0.90	100	100	100	100	100	100	100	100	100	100	100
0.85	105	103	104	105	104	103	104	104	103	104	104
0.80	108	107	108	108	108	108	108	108	108	109	109
0.75	110	111	112	113	113	115	113	112	111	109	112
0.70	116	115	116	116	119*	120	118*	117	116	118	115
0.65	121	123	122	122	125*	126*	124*	120	121	125	120
0.60	129	131	130	130	131*	133*	132*	126	128	126	124
0.55		140*	137	139	148*	152*	150*	130	132	126	130
0.50	150*	154*	152*	149*	130*	167*	127*	138	146	137	143
0.45	169*	173*	170*	178*		132*		150*	158	142	160*
0.40	185*	152*	160*	139*				167*	172*	165*	184*
0.35								191*	196*	187*	216*
0.30								222*	213*	210*	160*
0.25											

* Figures corrected for hemolysis.

The vertical columns indicate the percentage of swelling in the cells of each of the patients. In each cell type, two sets of heavy horizontal lines will be noted. These represent the points beyond which the cells no longer behave in a linear relationship.

tivity and osmotic fragilities may be proportional to changes in intracellular protein osmotic pressures of given cell types, for example, the "normal" red blood cells, the red blood cells found in congenital microspherocytosis, and the red blood cells of sickle cell anemia. Support for this supposition may be derived as follows:

If this value is measured graphically for the red blood cells found in sickle cell anemia it is found to correspond to a difference of —0.065% NaCl. This figure is equal to the difference between the intracellular protein osmotic pressure of normal cells and those of sickle cell anemia as determined by independent means, that is, by determinations of freezing points. Moreover, the differences between the osmotic fragilities of abnormal and of normal cells are of comparable magnitude (see schematic diagram, Fig. 4).

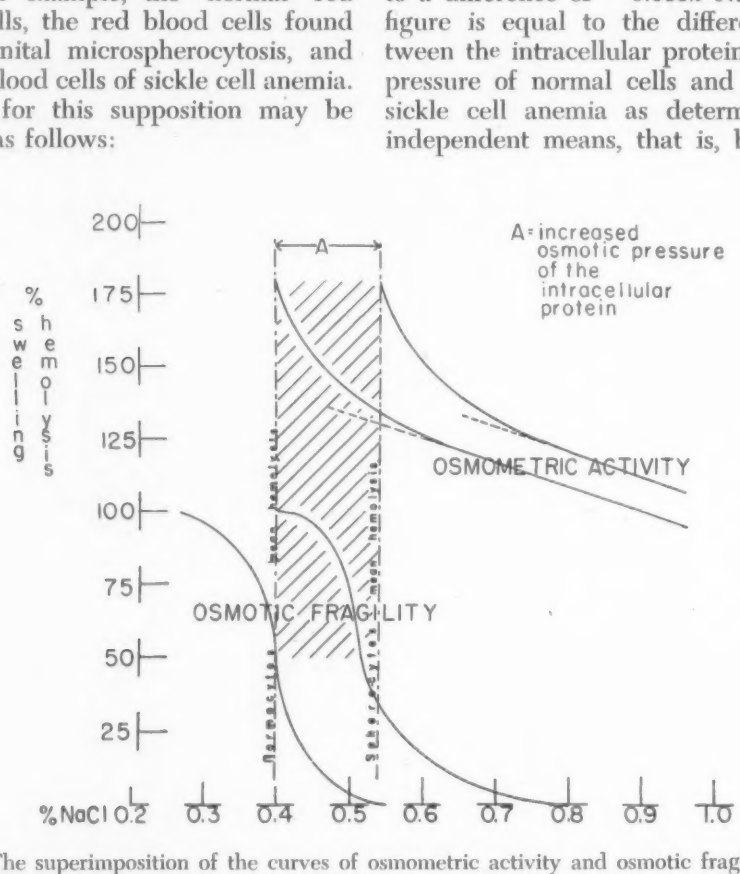

Fig. 4.—The superimposition of the curves of osmometric activity and osmotic fragility of the normocyte compared to the spherocyte. This is a schematic representation to illustrate that increased osmotic fragility and osmometric activity of the spherocyte when compared to the normocyte is due primarily to the increase of intracellular protein osmotic pressure. The vertical lines represent the mean hemolysis for the two red cell populations. Their arithmetical difference is equal to A, the increased intracellular protein osmotic pressure of the spherocytic population.

The distance d shown in Figs. 2 and 3, represents the hypotenuse of a right angle triangle, from which the differences in volume for the abnormal cell and the differences in osmotic pressures may be calculated.

$$a = \frac{dx}{dy} = \text{Tan } \theta$$

$dx = d \text{ Cos } \theta = d' =$ change in intracellular osmotic pressure

The results of osmometric activity of the red blood cells found in congenital spherocytosis are recorded in Table 3 and illustrated in Fig. 3. It is apparent that the increases in os-

mometric activity and osmotic fragility are proportional to the changes in the osmotic pressure of the intracellular protein.

There is probably some change in the protein osmotic activity during dialysis since by this procedure, more polar groups are exposed to the solvent. Conditions of this experiment attempted to keep such errors constant, that is, the final volume of each dialysate was approximately identical.

Hemolysis in acquired hemolytic anemia, on the contrary, is the result of loss of tensile strength of the membrane, since in this condition, increased mechanical fragility is not associated with any change in the intracellular osmotic pressure.

The cells of persons with the sickle cell trait reveal no abnormality except for decreased osmotic fragility of a small segment of the cell population.

The osmotic pressure of plasma of a normal person, as measured by depression of the freezing point, varies considerably at different times during a 24-hour period (Fig. 1). This variation seems to be initially dependent upon the amount of water ingested. It will be noted that within 15 minutes there is a rapid fall in plasma osmotic pressure proportional to the amount of water ingested. It is apparent that a large part of the water ingested is rapidly absorbed.

Summary. Results of the above experiments reveal that the normal erythrocyte functions as an imperfect osmometer within the range of osmotic pressure of normal plasma inasmuch as the changes in red blood cell volumes are related in linear fashion to changes in osmotic activity in the suspending medium.

Three variables in the production of hemolysis were mentioned in the introduction: 1) tensile strength of the cellular membrane, 2) intracellular osmotic pressure, and 3) extracellular osmotic pressure. One component of the intracellular osmotic pressure has been measured, namely, the intracellular protein osmotic pressure. Since the cell is in osmotic equilibrium with its environment, the osmotic pressure of the dialyzable material may be computed:

$$P_{rbc} - P_{prot} = P_{dial}$$

where P = the total osmotic pressure within the red blood cell, intracellular protein osmotic pressure, and the dialyzed material, respectively.

The destruction of normal erythrocytes in hypotonic solutions is apparently related to the intracellular protein osmotic activity of the individual cells. Those erythrocytes of a given population which have the highest intracellular protein osmotic activity are those which undergo hemolysis most readily, and those with the least intracellular protein osmotic activity are the most resistant to hemolysis in hypotonic solutions.

The plasma osmotic pressure to which the normal erythrocytes are exposed varies during the day.

The mean intracellular protein osmotic pressure of erythrocytes is relatively close to 0.19% NaCl in normal persons. The intracellular protein osmotic pressure is increased in congenital spherocytosis and decreased in sickle cell anemia. The change in intracellular protein osmotic pressure appears to be the critical variable in these hemolytic diseases. Essentially normal findings are present in all 3 variables in persons with the sickle cell trait, namely, 1) intracellular protein osmotic pressure, 2) extracellular osmotic pressure, and 3) membrane tensile strength.

Acquired hemolytic anemia is associated with increased mechanical fragility and normal intracellular osmotic

pressure, and thus appears to be the result of changes in the tensile strength of the membrane of the red blood cell.

The 3 variables which are related to hemolysis are constant in any given hemolytic disease, only one of the factors being distinctly different from normal in each hemolytic disease studied.

Conclusions. From the foregoing studies it may be concluded:

1) There is a normal daily variation in osmotic activity of plasma.

2) The red blood cell is in osmotic equilibrium with its plasma.

3) The intracellular protein osmotic pressure is increased in the red blood cells of the patients with congenital spherocytosis.

4) The intracellular protein osmotic pressure is decreased in the red blood cells of patients with sickle cell anemia.

5) The intracellular osmotic pressure is normal in the red blood cells of patients with sickle cell trait and in the red blood cells of patients with acquired hemolytic anemia.

6) Osmotic fragility of erythrocytes in genetic hemolytic anemias is dependent upon intracellular protein osmotic pressure and not on variations in the tensile strength of the cellular membrane.

7) In acquired hemolytic anemia, hemolysis is apparently the result of changes in the tensile strength of the membrane of the erythrocytes.

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ELECTROCARDIOGRAPHIC PATTERNS IN THE DIFFERENTIAL DIAGNOSIS OF PROGRESSIVE MUSCULAR DYSTROPHY

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Our interest in the electrocardiographic changes in cases of progressive muscular dystrophy was aroused 5 years ago by the observance of strikingly enlarged amplitudes in the QRS complexes of some of the precordial leads in a case of progressive muscular dystrophy with pseudohypertrophic features. In studying additional electrocardiograms, it soon became apparent that we could identify, almost with certainty, those patients in the pseudohypertrophic group merely by the increased amplitudes of the QRS complexes in one or more of the precordial leads.

Although a great deal of attention has been paid to the musculoskeletal system in cases of progressive muscular dystrophy, relatively little appears to have been given to detailed cardiac studies. It is recognized that the myocardium may be affected, but the incidence of such involvement has not been determined pathologically or clinically. Three recent papers[11,17,19] suggest that this is frequent. In the past 30 years comparatively few reports have appeared on the myocardial changes in this disease[1-3,5-12,17-19], and of these even fewer have dealt with electrocardiographic findings[1,3,5,6,10,11,18,19]. A comprehensive summary of the general aspects of the heart in progressive muscular dystrophy has recently been presented by Zatuchni and co-workers[19].

As pointed out by Tyler and his associates[15,16], many names have been associated with progressive muscular dystrophy, depending chiefly on which group of muscles was affected. Two clinical types are now generally accepted. The first, or childhood type, is often pseudohypertrophic, nearly always affects males, starts at a younger age, terminates in death at an early age, and is characterized clinically by muscular enlargement. The second type is rarely pseudohypertrophic, affects both sexes about equally, starts in late childhood or adolescence, and infrequently incapacitates before middle age. These authors have proposed that these 2 be classified as, (1) The Childhood Type, and (2) The Facioscapulohumeral Type.

Material and Methods. Nine cases of progressive muscular dystrophy have been studied at our institution. Seven of them are living, and two have expired. All have had electrocardiographic study. Six of the 9 belonged in the childhood or pseudohypertrophic group. The ages varied from 15 to 30 years in the pseudohypertrophic group, and from 21 to 43 years in the nonpseudohypertrophic group. There were 2 females, one in the pseudohypertrophic group, (Case 3), age 30 years; the other, (Case 7) age 43 years, in the nonpseudohypertrophic group.

Precordial leads on the living patients were made with the Wilson terminal electrode.

Unipolar extremity leads were augmented by the method of Goldberger. The values for normal voltage of ventricular deflections utilized here for comparative purposes were those recently published by Sokolow and Friedlander[14] for the V leads, and those published by Dolgin, Grau, and Katz[4] for the CF leads. Axis deviations were calculated by the method of Wenckebach and Winterberg[13].

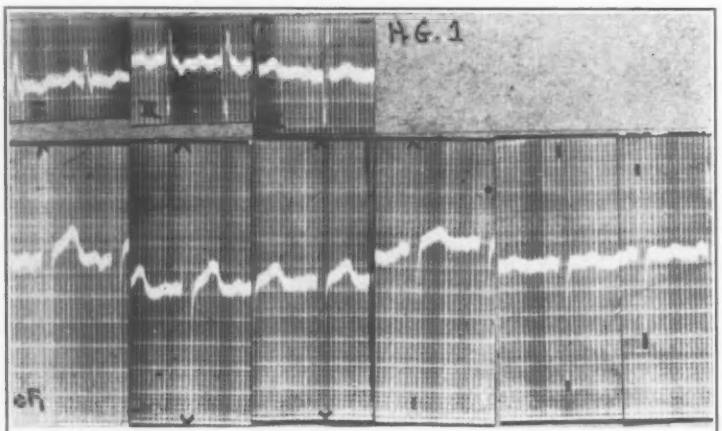

Fig. 1

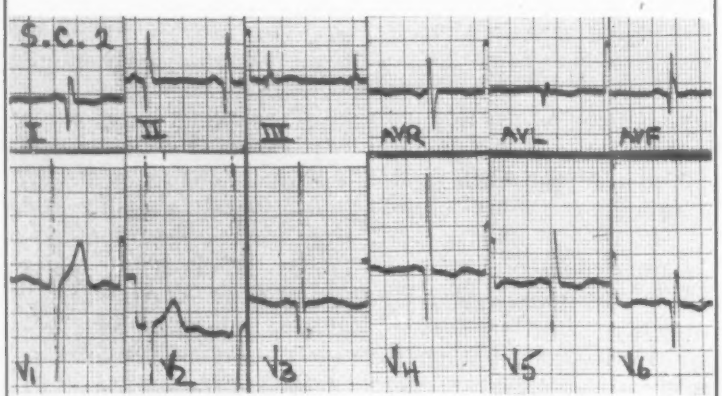

Fig. 2

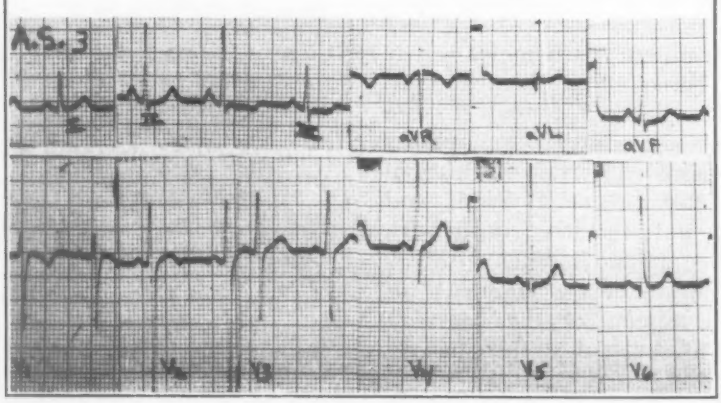

Fig. 3

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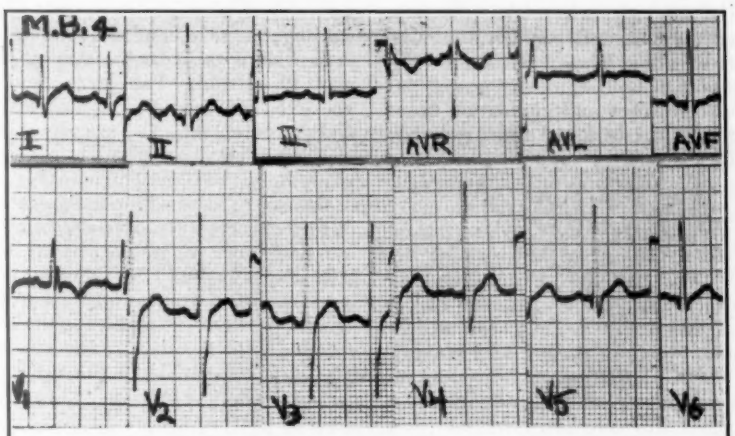

Fig. 4

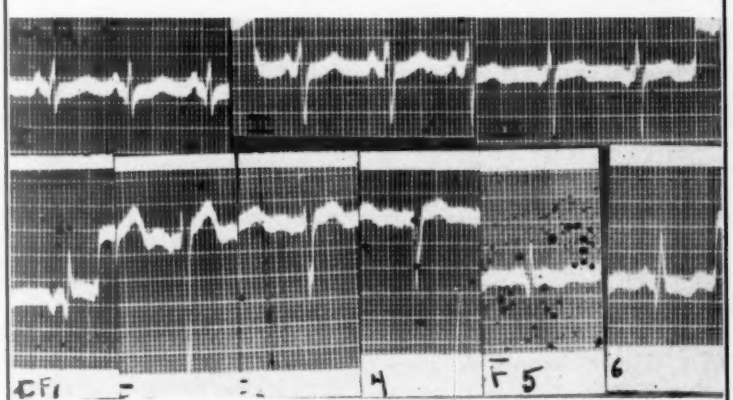

Fig. 5

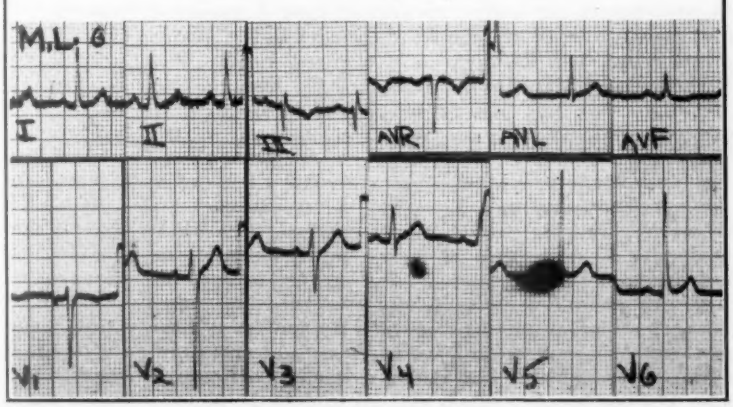

Fig. 6

Figs. 1–6.—Note increased height of QRS complexes in one or more of the precordial leads. These cases showed pseudohypertrophy.

In the patients still alive, roentgenographic examination of the heart was made. However, estimation of the size and configuration was not considered reliable because of skeletal deformities present in both clinical types of patient. Venous pressures and circulation times were so variable and little related to clinical data as to be considered unreliable.

Case Reports. CHILDHOOD OR PSEUDOHYPERTROPHIC TYPE. *Case 1.* H.G., a white male, was admitted at the age of 12 years and expired in 1946, at the age of 25 years, of left heart failure. The cardiovascular status was clinically normal except for moderate tachycardia with a rate of 100 per minute and frequent premature contractions. The electrocardiogram taken in 1946, 2 months prior to exitus, showed deep Q_3 and Q_3 and inverted T_1. The large QRS complexes in the precordial leads are shown in Fig. 1. Their excess over the published maximal normal values is given in Fig. 10.

Case 2. S.C., a 15-year-old white male, was admitted to the hospital at the age of 7 years. Physical examination revealed no cardiovascular abnormalities. The blood pressure was 118/70 mm. Hg, pulse 88 per minute, and venous pressure 143 mm. of water. The heart size was not calculable radiologically. The electrocardiogram showed deep Q of normal duration in leads 1, 2, avL, aVF, and across the left precordium, associated with inverted T waves in these leads with the exception of lead V_2. The abnormally large QRS complexes in the right sided precordial leads are shown in Fig. 2, their excess over the maximal normals in Fig. 10.

Case 3. A.S., a 30-year-old white female, was admitted at the age of 27 years. The onset of her illness was noted at the age of 7 years with weakness in the lower extremities. Physical examination of the heart revealed a gallop rhythm over the apex and a localized systolic murmur over the pulmonic area. The blood pressure was 135/90 mm. Hg, venous pressure 142 mm. of water, ether time 7 seconds, and Decholin time 11 seconds. The electrocardiogram revealed no abnormalities except large amplitude of QRS complex in lead V_2 (Fig. 3). The S wave in lead V_1, axis plus 60 degrees, is 29 mm., equal to the maximal normal (Fig. 10).

Case 4. M.B., a 20-year-old white male, was admitted to the hospital at the age of 13 years. There were no clinical cardiac abnormalities. The blood pressure was 110/80 mm. Hg, pulse 120 per minute, venous pressure 90 mm. of water, ether time 12 seconds, and Decholin time 22 seconds. In December, 1949, he expired in pulmonary edema following a short siege of pneumonia. The electrocardiogram taken in September, 1949, revealed sinus tachycardia with a QRS interval of 0.10 second. The large amplitude may be noted in the QRS complex in leads V_2 and V_3 (Fig. 4). The excess of 3 mm. beyond the maximal normal in lead V_2, axis plus 68 degrees, is shown in Fig. 10.

Case 5. M.R., a white male was admitted at the age of 17, and expired at the age of 21, in 1947, of congestive heart failure and bronchopneumonia. No clinical cardiac disease was noted. The electrocardiogram revealed Q waves in leads 1, CF_5 and CF_6 associated with inverted T waves in these leads. The large amplitude of the QRS complex in CF_2 is shown in Fig. 5. While the complex exceeds the mean normal, SCF_2 measured 27 mm., 3 mm. less than the maximal normal value.

At postmortem examination, the heart weighed 760 gm. The left ventricle measured up to 2.5 cm. in thickness, the right ventricle up to 7 mm. The cardiac muscle was dull gray red, mottled with grayish white areas, particularly in the posterior wall of the left ventricle. The endocardium was smooth and not thickened. Microscopically, the subepicardial fat was increased, and infiltrated between the muscle fibers. There were extensive areas of replacement fibrosis, particularly in the posterior wall of the left ventricle, which contained scattered areas of infiltration with monocytes and lymphocytes. The muscle cells that remained viable in the fibrosed areas showed marked hypertrophy of their fiber and nuclear hyperchromatism. The branches of the coronary arteries showed no histological changes.

Case 6. M.L., a 23-year-old white male was admitted to the hospital at the age of 13 years. Physical examination showed no cardiac abnormalities. The blood pressure was 122/78 mm. Hg, and the apical rate 92 per minute. He expired during an episode of lobar pneumonia. The electrocardiogram revealed a left axis shift, plus 34 degrees (Fig. 6). While no complex exceeded the maximal normal, R in lead V_5, was 22 mm., or 2 mm. less than that value (Fig. 10).

At postmortem examination, the heart weighed 360 gm. The thickness of the myocardium measured up to 1.7 cm. in the left ventricle and up to 0.5 mm. in the right ventricle. There were occasional grayish white scars in the posterior wall of the left ventricle. Microscopically, the subepicardial fat was moderately increased and extended occa-

sionally between fibers. The muscle fibers were thin and showed preservation of the cross striation in most areas. In the posterior wall of the left ventricle extensive replacement fibrosis was noted. Here the fibers revealed loss of cross striation and of distinct outline of the contour. The nuclei were occasionally pycnotic and distorted. There was moderate infiltration with occasional histiocytes and a few eosinophils. The endocardium

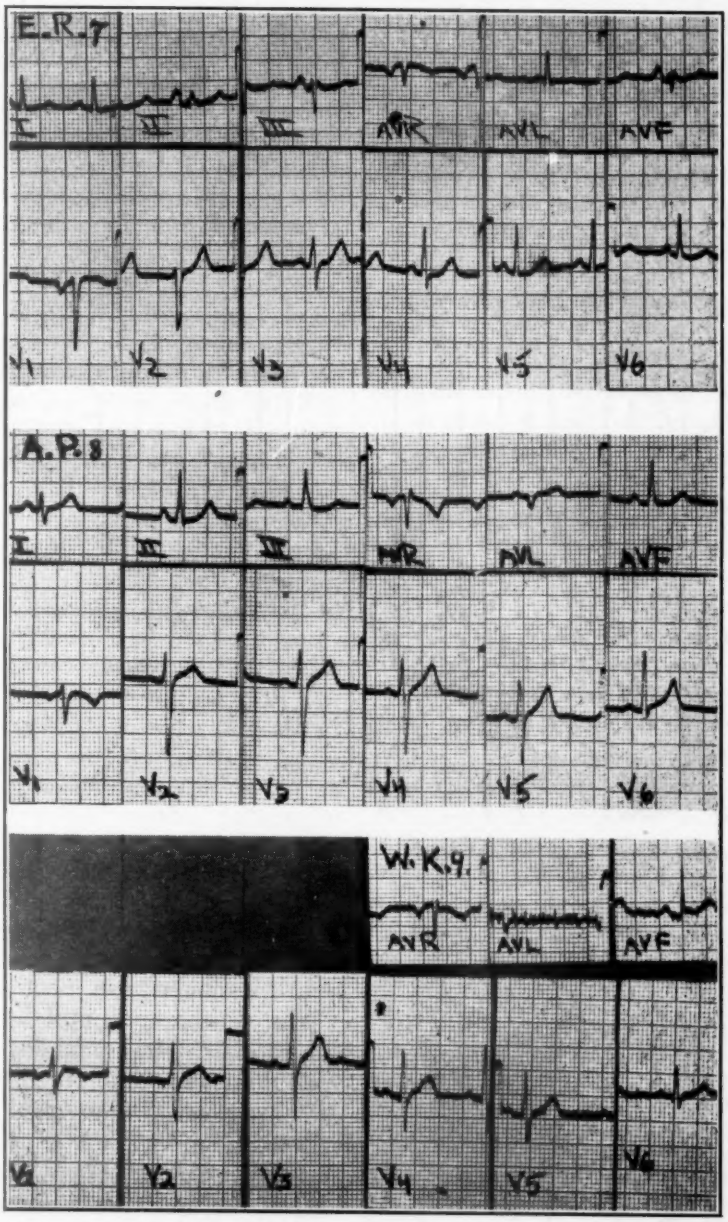

Fig. 7

Fig. 9

Figs. 7–9.—Note normal height of QRS complexes in all leads. These cases showed no pseudohypertrophy.

covering these areas was moderately thickened. The coronary arteries were histologically unaltered throughout.

FACIOSCAPULOHUMERAL OR NONPSEUDOHYPERTROPHIC TYPE. *Case 7.* E.R., a 43-year-old white female was admitted to the hospital at the age of 42 years with a history of the onset of muscular dystrophy at the age of 3 years. Physical examination showed no cardiac abnormality. The blood pressure was 148/90 mm. Hg, pulse 92 per minute, venous pressure 88 mm. of water, ether time 9 seconds, and the Decholin time 15 seconds. The diagnosis by the Neurological Service was progressive muscular dystrophy, nonhypertrophic type. The electrocardiogram was normal (Fig. 7). The precordial QRS complexes were not enlarged and were well below the maximal normal values.

Case 8. A.P., a 21-year-old white male, was admitted to the hospital at the age of 20 years with a history of the onset of illness at 18 years of age. A muscle biopsy confirmed the clinical diagnosis of progressive muscular dystrophy. Physical examination showed no cardiac abnormality. The blood pressure was 110/70, pulse 76 per minute, venous pressure 200 mm. of water, ether time 4 seconds, and the Decholin time 13 seconds. The electrocardiogram was normal (Fig. 8). The precordial QRS complexes were well below the maximal normal values.

Case 9. W.K., a 39-year-old white male, was admitted to the hospital at the age of 18 years with a history of onset of illness at the age of 7 years. Physical examination showed no cardiac abnormality. The blood pressure was 114/90 mm. Hg, the pulse 88 per minute, venous pressures and circulation time studies were not available. The electrocardiogram was normal (Fig. 9). The precordial QRS complexes were well below the maximal normal values.

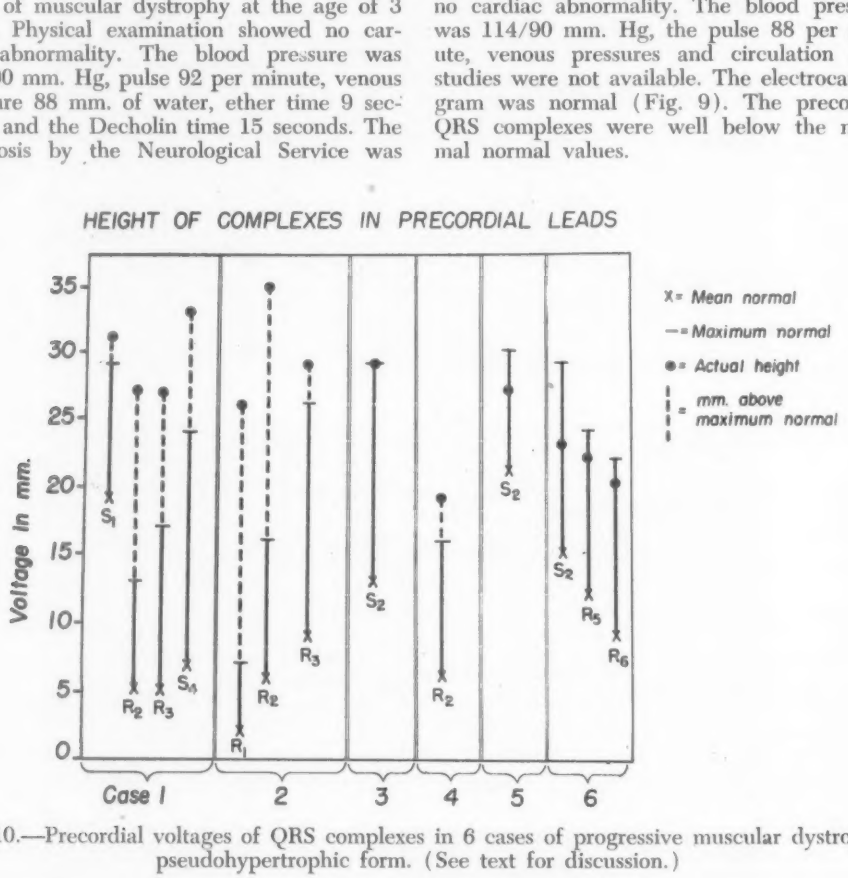

Fig. 10.—Precordial voltages of QRS complexes in 6 cases of progressive muscular dystrophy, pseudohypertrophic form. (See text for discussion.)

Discussion. Save for a casual reference in the recent paper of Weisenfeld and Messinger[18], no mention has been made of the increased amplitude of precordial QRS complexes in the pseudohypertrophic or childhood type of progressive muscular dystrophy. Each of our 6 cases in this category exhibited this finding, 4 cases exceeding by a significant margin the maximal normal values. These cases are in sharp contrast to those of the non-

pseudohypertrophic or facioscapulohumeral type. All our 3 cases in this latter category exhibited QRS complexes in the precordial leads approximating the mean normal figures. The reason for these high voltages in the former group is not apparent at the present time. Since skeletal deformities of approximately equal degree were present in patients in both categories, we do not believe that the electrocardiographic QRS complex differences can be attributed to this factor. Nor do we think that these differences in pattern can be attributed to pathologic changes in the heart of unrelated character since, in the cases coming to necropsy, no pathologic alterations were found except those of the dystrophic variety or their direct sequelæ.

Though Weisenfeld and Messinger[18] did not divide their cases into the two clinical forms of the disease, it is apparent from their data that the differentiation suggested by us obtains in their material. Thus 7 of their cases showing abnormally tall R waves in the precordial leads are classified as pseudohypertrophic. Of the other 6 cases in which no designation of the type is recorded, all were males and under 24 years of age. Of the 6 cases in which postmortem examinations were performed with pathologic evidence of dystrophic myocardial changes, one, clinically pseudohypertrophic in type, showed tall R waves in the chest leads. The others showed chiefly P wave changes, and these had either chronic pneumonic, pleuropericardial effusive, or chronic or active rheumatic myoendocardial pathology. Though muscular dystrophic changes were found in all 5 cases, the electrocardiographic alteration in all, except the one showing R wave alterations, appears compatible with the associated and independent pathology alone. None showed the excessively tall QRS complexes.

Summary. 1. Nine cases of progressive muscular dystrophy are presented with special reference to the electrocardiographic findings. Of these, 6 are of the childhood or pseudohypertrophic type.

2. The striking electrocardiographic feature in this series is the consistent occurrence of high voltage QRS complexes in one or more of the precordial leads. In 4 of the 6 cases these voltages exceeded the published maximal normals. In the other 2 cases they closely approach the maximum. Analysis of tracings in other published cases of this form of the disease discloses similar high voltage complexes.

3. These changes are not present in the 3 cases which showed no pseudohypertrophic features (facioscapulohumeral type). The QRS complexes in these cases approximate the mean normal published values.

4. This finding is suggested as a further differential feature in distinguishing clinically between the two groups of the disease.

To Dr. A. M. Rabiner, Director of the Neurological Service, go our thanks for the neurological data and for permission to use these cases, and to Dr. B. W. Volk, Director of Laboratories, for permission to use the pathologic data in Cases 5 and 6.

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THE DIAGNOSIS OF CARDIAC HYPERTROPHY IN THE AGED: CLINICAL PATHOLOGICAL CORRELATIONS IN 55 INDIVIDUALS

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The clinical determination of heart size in the aged is made difficult by the effects of the aging process on the heart and the chest wall, as well as by the increased incidence of associated diseases. In view of these difficulties, it was felt worthwhile to attempt to establish the accuracy of the methods commonly used by means of a clinical-pathological study of a group of aged individuals. As a preliminary to study of a larger series, this presentation compares the results in 55 elderly individuals of physical examination, chest film and electrocardiogram, as checked by the actual degree of cardiac hypertrophy found at necropsy.

Material and Methods. The clinical records of 55 consecutive cases coming to necropsy at the Kingsbridge House, a unit of the Home for Aged and Infirm Hebrews of New York, during the years 1950-1953, were completely analyzed. All had been given complete physical examinations at yearly intervals with 6-foot chest roentgenograms and electrocardiograms, in addition to those performed for specific complaints and illnesses. The patients comprised men and women ranging in age from 63 to 95 years; only 3 were below 70 and one above 90 years of age.

The following information was abstracted from the records:

1. The diagnosis of cardiac size on physical examination within 2 years of death. Notation was made of the diagnosis of enlargement or no enlargement without regard to degree. Examinations made in the immediate pre-mortem stage were excluded to eliminate the effect of terminal cardiac dilatation.

2. The diagnosis of cardiac size on 6-foot chest roentgenogram within 2 years of death. Notation was made of the diagnosis of enlargement or no enlargement. Numerical measurements were not employed as the cardio-thoracic ratio was not felt sufficiently accurate, and height and weight at the time of Roentgen-ray examination were not available, making the use of tables based on them impracticable. These diagnoses were made by the same staff roentgenologist who has had extensive experience in the interpretation of films in this age group.

3. The diagnosis of cardiac hypertrophy by electrocardiographic criteria on tracings taken within 2 years of death. All tracings taken within this period were analyzed according to the criteria for hypertrophy as well as for the presence of other abnormalities. All records included leads I, II, III, aVR, aVL, aVF and V_2, V_4 and V_5, and were taken in the supine position with a Sanborn direct writing electrocardiograph. The standardization (1 cm. = 1 mv.) was checked in all cases and where necessary proper calibration correction was made. The amplitude of the R and S waves was measured from the top and bottom of the base line to the highest and lowest portion of the deflection respectively. The time of onset of the intrinsicoid deflection was measured from the onset of the QRS to the peak of the R wave.

The presence of one or more of the following criteria for left or right ventricular hypertrophy was noted.

A. Left ventricular hypertrophy (with a horizontal heart).
   1) The sum of the amplitude of R in lead I plus S in lead III equals or exceeds 25 mm. ($R1 + S3 = \text{or} > 25$).
   2) The amplitude of R in aVL exceeds 11 mm. ($RaVL > 11$).
   3) The amplitude of R in V_4 exceeds 26 mm. ($RV_4 > 26$).
   4) The amplitude of R in V_5 exceeds 26 mm. ($RV_5 > 26$ mm.).
   5) The time of onset of the intrinsicoid deflection in V_5 exceeds 0.05 second ($ID > 0.05$).

These criteria correspond to those outlined by Sokolow and Lyon[9], with the following

modifications due to the absence of precordial leads V_1, V_3 and V_6 in our material. Criteria 3 and 4 use leads V_4 and V_5 instead of V_5 and V_6. It was felt that this was a reasonable substitution as the maximal normal voltage of the R wave in leads V_3 through V_6 in the normal aged vary only to a small degree, V_3 25 mm., V_4 30 mm., V_5 25 mm., and V_6 22 mm.[6], and when the factor of variation in electrode position with the common conditions of senile emphysema and kyphoscoliosis and dorsoscoliosis in the aged is taken into account.

In criterion 5 the intrinsicoid deflection in V_5 alone is used, where they[9] use V_5 and V_6.

We did not employ their sixth criterion involving the sum of deepest S in V_1 or V_2 and the tallest R in V_5 or V_6 exceeding 35 mm., as V_1 and V_6 were not available.

B. Left ventricular hypertrophy (with a vertical heart).
   1) The amplitude of R_2 plus R_3 exceeds 40 mm.[2].
   2) The amplitude of R in aVF exceeds 20 mm.[2,8].

C. Right ventricular hypertrophy.
   1) R in lead aVR exceeds 5 mm.
   2) The R/S ratio in V_5 is one or less.
   3) The S in V_5 exceeds 7 mm.
   4) The intrinsicoid deflection in V_2 equals or exceeds 0.04 second.

These were modified from those of Sokolow and Lyon[9] in that in criterion 2, V_6 could not also be used; also similarly in criterion 3; and that due to the absence of V_1, V_2 was used in criterion 4 in determining the intrinsicoid deflection from the right side of the heart.

Their additional criteria involving the height of R in V_1 exceeding 7 mm., and the R in V_1 plus the S in V_5 exceeding 10.5 mm. were not employed.

The criteria for hypertrophy based on the configuration of the S–T segments and T waves were not employed in this study because of the high frequency in this age group of conditions other than hypertrophy causing alteration of these components of the electrocardiogram. One or more positive criteria in any electrocardiogram in the 2 years preceding death classified the case as revealing hypertrophy.

4. The diagnosis of cardiac hypertrophy on postmortem examination with regard to degree, that is, slight, moderate, marked or none, and to chamber, namely, right or left ventricular.

The gross and microscopic interpretations of these necropsies were made by Dr. Joseph C. Ehrlich, Pathologist of the Kingsbridge House, a unit of the Home for the Aged and Infirm Hebrews. The heart weights were obtained with 4 cm. of aorta attached and free of pericardial fat and pericardium. Measurements of the width of the ventricular muscle from the base of the left ventricle were examined in all cases. From this material an over-all impression as to the existence of right and left ventricular hypertrophy was made and classified as to degree as above.

The protocols were also studied for information as to the presence and extent of coronary sclerosis, narrowing and occlusion. The presence of recent or old coronary occlusion and myocardial infarction was noted. The degree of myocardial fibrosis and the presence of ventricular aneurysms were recorded.

Cardiac weight was not employed as the basic criterion of the degree of hypertrophy for a number of reasons. Heart weight in addition to sex variation, a known factor here, is most closely correlated with body weight and also to a degree with height[16]. This information was not available to us at necropsy. There are additional objections to the use of heart weight as a criterion of hypertrophy. Terminal illness with cachexia and malnutrition cause marked cardiac atrophy[4]. The effect of increasing age itself on heart weight as distinguished from that of terminal cachexia from neoplasms and debilitating illnesses is subject to a considerable difference of opinion in the literature with variation upwards, downwards and no change at all being reported[16]. The question of change in the amount of intracardiac deposition of fat with age is also unsolved.

In the over-all impression as to the degree of cardiac hypertrophy the findings on gross examination were given greatest weight as it was realized that only sections of a relatively small area of myocardium were studied. The phenomenon of compensatory hypertrophy of muscle fibers in areas adjacent to myomalacia, a common condition in this group, was also considered as diminishing the reliability of the microscopic examination.

Results. The results of this study are tabulated in Tables 1 through 5.

As a group those with hypertrophy at postmortem examination represented left ventricular hypertrophy. There were only 2 cases with a slight degree of right ventricular hypertrophy and both had concomitant left ventricular

hypertrophy of a predominant nature. In no case did the radiologist diagnose right ventricular enlargement and all of the positive criteria for hypertrophy in the electrocardiograms were those of left ventricular hypertrophy with a horizontal heart. In no case was mention made on physical examination of any finding indicating a suspicion of enlargement to the right, or of the tion of records obtained during the terminal episodes in some cases. The electrocardiographic patterns in those with moderate or marked hypertrophy showed a high incidence of abnormalities in addition to the positive criteria for hypertrophy.

The results shown in Tables 1 and 2 can be summarized as showing a division into 2 fairly well differentiated

TABLE 1.—CLINICO-PATHOLOGICAL COMPARISON OF THE GROUPS WITH VARYING DEGREES OF LEFT VENTRICULAR HYPERTROPHY

	Degree of Hypertrophy			
	None	*Slight*	*Moderate*	*Marked*
Number of cases	16	7	21	11
Average age	81.0	81.5	78.3	78.5
Average heart weight	304	325	426	529.8
Range of heart weights	150–410	225–430	225–560	360–810
Average heart weight: males	336	335	417	564
Average heart weight: females	283	300	428.5	501.3
Average blood pressure	162/89	142/79	201/104	203/101
No. with blood pressure over 150/90*	8	1	20	7

* Of the 22 females in the group with moderate or marked hypertrophy, 21 had elevated blood pressures.

TABLE 2.—COMPARATIVE INCIDENCE OF CORONARY ARTERY AND MYOCARDIAL PATHOLOGY

	Degree of Hypertrophy	
	No or Slight Hypertrophy	*Moderate or Marked Hypertrophy*
Total number of cases	23	32
Pathological evaluation of degree of coronary atherosclerosis	11 with little coronary atherosclerosis	9 with little coronary atherosclerosis
Pathological evaluation of degree of myocardial fibrosis, old infarction and aneurysm formation	11 with little myocardial change	9 with little myocardial change
Essentially normal heart on pathological examination	5	4

right ventricle. When considered individually, the bulk of the individuals in the no and slight hypertrophy groups had normal or borderline blood pressure levels while those in the moderate and marked hypertrophy group had hypertensive levels.

The electrocardiograms in all of the cases with no or slight hypertrophy were essentially normal with the exceptions groups, one with no or slight hypertrophy, and one with moderate or marked hypertrophy at postmortem examination. The former is composed of normotensives with basically normal electrocardiographic patterns. The latter is composed predominantly of hypertensives with abnormal basic electrocardiographic patterns. The former group has a considerably smaller

incidence of severe coronary and myocardial disease and an appreciable incidence of normal hearts.

A survey of the results of the accuracy of physical examination in the detection of cardiac enlargement is shown in Table 3. In the groups with no or slight left ventricular hypertrophy at postmortem examination only one of 23 cases was diagnosed as being enlarged while 20 of 32 with moderate or marked hypertrophy were so diagnosed with an increasing accuracy with increase in degree of hypertrophy.

TABLE 3.—INCIDENCE OF DIAGNOSES OF CARDIAC ENLARGEMENT ON PHYSICAL EXAMINATION AND CHEST ROENTGENOGRAM AND OF HYPERTROPHY BY ELECTROCARDIOGRAPHIC CRITERIA

Postmortem Evaluation of Degree of Left Ventricular Hypertrophy	*Enlarged Heart on Physical Examination*	*No. of Cases*	*Enlarged Heart on Chest Roentgenogram*	*No. of Cases*	*Left Ventricular Hypertrophy by Electrocardiographic Criteria*	*No. of Cases*
No hypertrophy	1	16	6	13	0	13
Slight hypertrophy	0	7	0	6	0	6
Moderate hypertrophy	12	21	11	16	12	21
Marked hypertrophy	8	11	8	8	7	10

A survey of the results of the accuracy of the chest roentgenogram in the detection of cardiac enlargement is shown in Table 3. In the cases with no or slight hypertrophy at postmortem examination, there were 6 of 23 diagnosed as showing enlargement on chest roentgenogram; all of these 6 cases had no diagnosis of enlargement on physical examination or of hypertrophy by electrocardiographic criteria. In the cases with moderate or marked hypertrophy 19 of a total of 24 had cardiac enlargement on chest roentgenogram, including all with marked hypertrophy.

The results of the accuracy of the electrocardiographic criteria for hypertrophy are also shown in Table 3. All of the positive criteria were for left ventricular hypertrophy with a horizontal heart position. No positive criteria were found for either left ventricular hypertrophy with a vertical heart position or for right ventricular hypertrophy.

No positive criteria for hypertrophy were found in the no or slight hypertrophy groups. In the moderate or marked hypertrophy groups 19 of a total of 31 cases had positive criteria.

An analysis of the individual cases revealed no absolute relationship between the cases diagnosed as enlarged or hypertrophied by the 3 methods used in this series. There was a trend for the enlarged hearts on physical examination and chest roentgenogram to occur in the same cases more frequently than either with positive electrocardiographic criteria for hypertrophy. There was also a greater frequency of cases with diagnoses of enlargement on chest roentgenogram without electrocardiographic criteria of hypertrophy than *vice versa*, in the groups with moderate and marked hypertrophy.

In Table 4 is an analysis of the sensitivity of the electrocardiographic criteria employed in the diagnosis of hypertrophy in this study.

The two predominant criteria were RaVL greater than 11 mm. and R1 + S3 = 25 mm. or greater both being positive in about 40% of the cases with one or more positive criteria.

In Table 5 is an analysis of the overall accuracy of detection of the three

methods used. No case of slight hypertrophy at postmortem examination was diagnosed in life by any of the methods used. In the groups with moderate or marked hypertrophy all were diagnosed in life by one or more of the 3 methods employed. The percentage diagnosed by 2 or 3 methods increased with the increase in the degree of hypertrophy. Where only one clinical method of diagnosis was positive, diagnosis by electrocardiographic criteria predominated. Where more than one was positive, cardiac enlargement on chest roentgenogram was predominant.

TABLE 4.—SENSITIVITY OF ELECTROCARDIOGRAPHIC CRITERIA COMPARED WITH POSTMORTEM EVALUATION OF DEGREE OF LEFT VENTRICULAR HYPERTROPHY

Electrocardiographic Criteria	*No or Slight Hypertrophy*	*No. of Cases*	*Moderate Hypertrophy*	*No. of Cases*	*Marked Hypertrophy*	*No. of Cases*
I.D. V5 > 0.05 sec.	0	16	3	21	2	10
R1 + S3= 25 mm. or >	0	16	7	21	5	10
RaVL > 11 mm.	0	16	9	21	4	10
RV4 > 26 mm.	0	16	4	21	3	10
RV5 > 26 mm.	0	16	1	21	4	10

TABLE 5.—THE CLINICAL ACCURACY OF DETECTION OF CARDIAC HYPERTROPHY

CORRELATION OF THE DEGREE OF HYPERTROPHY AT POSTMORTEM EXAMINATION WITH DIAGNOSIS OF ENLARGEMENT BY PHYSICAL EXAMINATION AND CHEST ROENTGENOGRAM AND OF CARDIAC HYPERTROPHY BY ELECTROCARDIOGRAPHIC CRITERIA

Degree of Hypertrophy	*Slight*	*Moderate*	*Marked*
Number of cases*	4	16	8
Undiagnosed by all three methods	4	0	0
Diagnosis made by one method only	0	4	1
Diagnosis made by two methods	0	9	3
Diagnosis made by all three methods	0	3	4

*Cases in which the results of all three methods of diagnosis were available.

Discussion. The high incidence of hypertensive blood pressure levels in the groups with moderate or marked hypertrophy is not surprising in view of the well-known correlation between the occurrence and severity of hypertension and the occurrence and degree of cardiac hypertrophy[10].

The increased incidence of coronary and myocardial pathology in the groups with moderate or marked hypertrophy is a reflection of the higher incidence among them of such causative factors for coronary disease as hypertension and calcific aortic stenosis.

The normality of the electrocardiograms in the groups with no or slight hypertrophy is surprising in view of the findings at postmortem examination of a considerable degree of coronary disease and myocardial fibrosis in approximately half of them, despite the known fact that a clinically normal heart may show coronary sclerosis and myocardial fibrosis at necropsy[7]. This may be a function of the small size of this series and will be given special attention in the further extension of the study.

The average weights of the male and female hearts in the no hypertrophy group agreed well with average normal weights previously reported for this age group[16].

In evaluating the results obtained by physical examination and chest roentgenogram, it must be understood that these methods give their results

in terms of enlargement, which is a matter of dimensions and does not necessarily correspond to cardiac hypertrophy. A dilated heart is a large heart, but its degree of hypertrophy does not necessarily correspond to its increased size. Dilatation is common in the aged as shown by Howell and Piggot[5] who found it in 18% of 164 cases over age 80 at postmortem examination.

There are a number of other factors complicating the diagnosis of cardiac enlargement by physical and roentgenographic examinations which are particularly significant in the aged. The latter have been described by Olbrich[6]. There is a forward bending of the vertebral column with aging which may cause a loss of height up to 6 to 8 cm., due to shrinkage of the intervertebral discs and decreased height of the vertebral bodies due to eccentric atrophy, especially of their anterior surfaces. The resultant kyphoscoliosis is frequently accompanied by a dextroscoliosis which makes definition of the right heart border difficult by Roentgen ray. Loss of elasticity and atrophy of lung tissues cause senile emphysema with a greater distance from the heart to the chest wall. Elongation and tortuosity of the aorta may alter the position of the heart by rotation, with the base of the heart serving as a fulcrum. The diaphragm is lower in the aged. Diaphragmatic herniae may alter the position of the heart. An increased incidence of fibroid tuberculosis, atelectasis and pneumothorax also serves to confuse the issue. Pendulous breasts impair the accuracy of diagnosis, as does the extrapericardial fat pad. The contour of the chest cage itself may be altered by ossification of the costal cartilages with greater rigidity of the cage, and, with the above changes in the spine, yields a chest with a longer A–P diameter, a shorter transverse diameter, and a greater lower circumference. The accumulation of pericardial fluid with heart failure adds an additional diagnostic difficulty.

In view of these difficulties the accuracy of diagnosis on physical examination in this series is impressive. The majority of those with moderate or marked hypertrophy at necropsy were detected and only one with no hypertrophy was diagnosed as enlarged where no hypertrophy existed at postmortem examination. Those with a slight degree of hypertrophy were not detected.

It is of interest to note that while White[13] has stated that one should be able to detect a heart weighing over 415 gm. on physical examination, only 15 of 23 hearts in this group which exceeded this weight at postmortem examination were so diagnosed.

The high incidence of diagnoses of enlargement on chest roentgenogram in the group with no hypertrophy at necropsy can best be explained by the factor of dilatation noted above[5]. Hellerstein[4] in his series of cases with cardiac atrophy found many of the smallest hearts at postmortem examination to have larger transverse diameters and cardio-thoracic ratios on chest roentgenogram than the heavier hearts in his series. He attributed this phenomenon to dilatation. Dilatation may also play a part in the high incidence of positive diagnoses of enlargement in the moderate and marked hypertrophy groups.

The results of the evaluation by electrocardiographic criteria are of interest in that there were no false positives, that is, the electrocardiogram did not reveal hypertrophy in life where none existed at postmortem examination; it was of no avail in those with slight hypertrophy and detected about 60% of those with moderate or marked hypertrophy.

These figures gain additional signifi-

cance when one considers the special situation presented by the aged. It has been stated that the standards of normality of QRS voltages differ in the normal aged from normals of other age groups, in that there is a progressive decrease in voltage with increasing age[3]. However, the largest series of normal aged in an age group approximating the one studied here, that of Olbrich[6], fails to reveal such a change. He studied 154 normals over age 60 and found no significant decrease in voltages compared to younger age groups of normals. A study of Vaquero's paper[11], which has been quoted as showing such a decrease reveals only a very small number of cases over 60 years of age.

Factors which impair the usefulness of these criteria are the prevalence of emphysema in the aged causing a decrease in voltage due to the increased heart-chest wall distance. This is compensated for by the prevalence of thin chest walls in the aged due to tissue and weight loss with age. Cardiac atrophy[4] is frequently accompanied by low voltage electrocardiograms. The increasing incidence of coronary disease is an important factor in diminishing the number of cases which can be diagnosed by this means. Willius[14] has shown that 75.5% of individuals over the age of 70 have moderate to advanced coronary atherosclerosis.

Coronary disease acts in several ways. Gradual increase in diffuse myocardial fibrosis causes a loss of voltage. We have seen this in studying the serial records of some of our cases and it has been reported in detail[12]. Myocardial infarction, bundle-branch block and coronary insufficiency, which are frequent in this age group, make useless the electrocardiographic diagnosis of hypertrophy by S–T segment and T wave changes which have been found of value in younger age groups. The use of digitalis by a considerable number and metabolic derangements act similarly. It was appreciated that occasional normals are to be found with voltages exceeding the limits of normality accepted for this series.

Comparison with other published material in the aged is made difficult by differences in groups by age, origin and variations in the number and types of criteria employed. Weinberg *et al.*[12] in a group of 95 cases coming to necropsy with an age range of 40 to 80 years found a comparable incidence of diagnosis of hypertrophy by electrocardiographic criteria. Wosika[15] in a group of 100 cases over 80 years of age also found a comparable incidence of electrocardiographic detection of hypertrophy, but found fewer normal records. Dolgin[1] in 71 aged persons studied in life found a comparable incidence of electrocardiographic evidence in those with hypertrophy.

The predominance of criteria RaVL >11 and $R1 + S3 = 25$ or greater as to sensitivity has been noted as being characteristic of the aged by other authors. Wosika[15] in his series of aged found 9 cases with RaVL positive and the criteria based on V_1 to V_6 negative. Heine[3] noted that RaVL and $R1 + S3$ were positive predominantly in those of his cases over the age of 40. Our criteria based on V_1 to V_6 are low in sensitivity by comparison with a group of a young age, as Heine's[3].

This difference in sensitivity of the criteria may be explained by a change in electrical position of the heart with aging. A shift toward a horizontal position with counter-clockwise rotation would produce a situation wherein the predominant voltages in left ventricular hypertrophy would be transmitted to lead aVL and away from the V leads over the precordium. The standard leads would reflect these changes with increased left axis deviation and

the expression of left ventricular hypertrophy by the criterion R1 + S3 = 25 or greater. Another aspect of this change in electrical position of the heart is manifested by the absence of any criteria for left ventricular hypertrophy with a vertical heart position in this series of the aged.

The higher coincidence of cases with positive diagnoses of enlargement on physical examination and chest roentgenogram than of either with cases having positive electrocardiographic criteria for hypertrophy is expected, as the former two are measures of size while the latter is a measure of hypertrophy *per se*.

In contrast to Sokolow's series[9], the number of cases with moderate or marked hypertrophy with enlargement on chest roentgenogram having negative electrocardiographic findings exceeded the number with positive electrocardiograms and negative findings on chest roentgenograms. This may be explained by the fact that ours is a consecutive series without exclusions while theirs, as well as Heine's[3], excluded all cases with known coronary disease, angina, bundle-branch block, Q waves suspicious of infarction and a history of having taken digitalis or quinidine. The known high incidence of such conditions in an older age group would be sufficient to decrease the number of positive electrocardiographic criteria sufficiently to cause the above situation.

Summary and Conclusions. 1. In an effort to assess the accuracy of clinical methods of detecting cardiac enlargement or hypertrophy in elderly patients, the findings on physical examination, chest film and electrocardiogram in 55 men and women ranging in age from 63 to 95 years have been correlated with observations at necropsy.

2. The diagnosis of cardiac enlargement or hypertrophy was made correctly in 32 cases, all of whom were found to show moderate to marked hypertrophy of the ventricular muscle at postmortem examination.

3. Slight hypertrophy of the ventricular muscle was demonstrated in 7 cases at postmortem examination but was not detected by any of the three clinical methods of examination.

4. In 16 cases without any hypertrophy of the ventricular muscle at postmortem examination, 6 were diagnosed as showing cardiac enlargement on roentgenogram and one on physical examination. Cardiac dilatation was considered as the probable cause of these diagnoses. None of this group manifested any of the electrocardiographic changes indicating cardiac hypertrophy.

5. In the 32 cases with moderate or marked hypertrophy of the ventricular muscle at necropsy, 20 of 32 were diagnosed as showing enlargement on physical examination. Nineteen of 24, where roentgenograms were available, were diagnosed as showing enlargement on chest film. Nineteen of 31, where electrocardiograms were available, were diagnosed as showing cardiac hypertrophy by electrocardiographic criteria. All were diagnosed as showing enlargement or hypertrophy by one or more of the three methods.

6. The most sensitive electrocardiographic criteria for hypertrophy were RaVL greater than 11 mm. and R1 + S3 = 25 mm. or greater. This was attributed to the increased electrically horizontal position and counterclockwise rotation of the heart associated with aging.

7. There was no consistent pattern of co-existence of diagnoses of enlargement or hypertrophy by the three methods in the cases with moderate or marked hypertrophy of the ventricular muscle at postmortem.

8. In the cases with moderate or

marked hypertrophy at postmortem examination, diagnoses of enlargement by roentgenogram and physical examination tended to occur more frequently in the same individuals than of either with hypertrophy by electrocardiographic criteria. This was attributed to the fact that the former are measures of size, the latter of hypertrophy.

9. In the cases with moderate or marked ventricular hypertrophy at necropsy, individuals with enlargement on roentgenogram and no positive electrocardiographic criteria of hypertrophy were more frequent than the reverse. This was attributed to the effects of the increased incidence of coronary and myocardial disease in this age group in diminishing the accuracy of the electrocardiographic criteria of hypertrophy.

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THE CURRENT STATUS OF ANTICOAGULANTS IN THE TREATMENT OF MYOCARDIAL INFARCTION

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ALTHOUGH anticoagulants have been used in the treatment of myocardial infarction since 1946, there is still considerable controversy concerning their value and the indications for their use. Wright[162], as Chairman of the American Heart Association Committee on Anticoagulants, and others, advocate anticoagulant therapy with Dicumarol or similar drugs for most cases of myocardial infarction. Some believe that anticoagulant therapy should be limited to "poor risk" patients, and still others have stated that Dicumarol is of no value in infarction. As of the date of publication, 1953, approximately half of the physicians responding to a survey made by Russek and Zohman[119] used Dicumarol routinely and half did not, although since the subsequent appearance of a number of favorable reports more may be using Dicumarol. Furthermore several editorials in leading medical journals[41-44] have indicated an unwillingness to accept completely the recommendations of the American Heart Association Committee, and have pointed out disturbing or puzzling features in the picture. If Dicumarol were a safe drug for general use, the controversy might have little importance. However, Dicumarol has caused a considerable number of fatalities. In this connection, the survey of Russek and Zohman[119] is of interest. Of the 228 physicians who answered their questionnaire, 28.1% observed at least one death due to anticoagulant drugs, and a total of 122 deaths was reported. Unfortunately, it is not clear whether or not duplication is involved in these figures, with more than one physician reporting on a single case. Furthermore, the circumstances of these

deaths are not given, and it is possible that many of them occurred early in the history of Dicumarol usage, before adequate laboratory tests of prothrombin time were available. Today the risk may well be less.

It is, therefore, important to attempt to define as precisely as possible the actions, area of usefulness, and dangers of these drugs.

This discussion will be concerned only with heparin and Dicumarol, since insufficient work has been done on their analogues to warrant review. Heparin is an anticoagulant *in vivo* and *in vitro*. Its action can be demonstrated as readily in a glass test tube as in an intact animal or human. Unfortunately, little is known about the effects of heparin in myocardial infarction. Most of the studies on anticoagulant therapy involved the use of heparin in a variable proportion of cases, for a brief time until the desired effect of Dicumarol on the prothrombin time had developed. Thus, when most authors refer to anticoagulant therapy in myocardial infarction they mean therapy with Dicumarol or related drugs, supplemented during the first day or two with heparin.

In evaluating the role of Dicumarol in myocardial infarction it is appropriate to consider not only the reports of its use in this condition, but also its pharmacology insofar as it is known and, briefly, the clinical experience with it in the treatment of other thromboembolic phenomena.

PHARMACOLOGY OF DICUMAROL. Dicumarol administration results in a lowering of the prothrombin content of the blood, probably by inhibiting its formation by the liver, although other actions may play a part. It also reduces the amount of Factor VII (S.P.C.A., convertin) in the blood[14a]. Dicumarol, unlike heparin, does not have an anticoagulant action on blood *in vitro*, and there is a delay of 24 to 48 hours before the effects of Dicumarol are manifested as a significantly lowered blood prothrombin content. Since prothrombin is essential to the clotting mechanism, a sufficient reduction in its concentration will decrease blood coagulability. It is well known, for example, that Dicumarol was discovered because cows ingesting it in spoiled sweet clover bled to death. There have been a number of studies on other animals[24,32,70,75,99,113] which showed that, in large amounts, Dicumarol increases clotting time. The doses of Dicumarol used clinically, however, which are much smaller than those used in the animal studies, do not ordinarily change the clotting time of the blood as measured by the Lee-White glass test tube method. The question has, therefore, been raised by Dietrich[29], Wheeler[29] and Ferguson[30] as to whether Dicumarol in clinical doses is in fact an anticoagulant. This question may be put somewhat differently: Is there any significant margin between the effective anticoagulant dose of Dicumarol and the dose which produces hemorrhage? This point must be scrutinized carefully, since it is a crucial one. The fact that large doses of Dicumarol interfere with coagulation does not necessarily prove that smaller doses will have a similar action to a lesser extent. There are several drugs which act one way in a particular dose range, but which may have a different action when given in a different dose range. In order to evaluate the effectiveness of Dicumarol as an anticoagulant, an understanding of the relationship of prothrombin content to the speed of clotting is essential. The blood contains a considerable excess of prothrombin over that required for normal coagulation. Thus, a moderate reduction in prothrombin may not affect the clotting process. Quick[107,108] showed that the coagula-

tion time is relatively little delayed until the prothrombin concentration drops below 20% of normal. This, of course, does not necessarily exclude the possibility that lesser reductions in blood prothrombin may alter intravascular clotting. The proponents of Dicumarol have pointed out that with therapeutic doses the coagulation time as measured in lusteroid or silicone tubes is prolonged[89, p.53;92]. They consider the glass surface used in the Lee-White test too crude for accurate measurement of blood coagulability. Certainly a glass surface is not the same thing as the endothelium lining a blood vessel, or the surface of a small thrombus. On the other hand, Ferguson[30] has pointed out that lusteroid and silicone are not necessarily more physiological than glass. A recent report adds emphasis to this by suggesting that silicone surfaces may be even less suitable than glass for accurate measurements of blood coagulability. Waldron, Knox and Duncan[144] have shown that silicone itself possesses anticoagulant properties. They state: "The addition of silicone to plasma in a glass container produces an incoagulable plasma and a visible protein precipitate. This suggests that silicone may inactivate an accelerator of coagulation by protein precipitation." It is conceivable that small doses of Dicumarol, in themselves unable to effect coagulation, can potentiate the anticoagulant action of silicone. Accordingly, it seems unlikely that the question whether Dicumarol in clinical doses is an anticoagulant is answerable by experiments on artificial surfaces. It is therefore appropriate to consider next the animal experiments with this drug.

ANIMAL EXPERIMENTS. As has been pointed out, a number of studies were performed using doses of Dicumarol which were far in excess of the clinically safe range, and which proved fatal to many of the animals. Since there is no question about the anticoagulant action of Dicumarol in high dosage, these studies require no further comment. However, some animal experiments were performed using the equivalent of clinical dosage ranges. Bingham, Meyer and Pohle[16] used monolate to produce intravascular clotting. In 12 animals treated with Dicumarol, the average intravascular clotting time was 16.4 minutes as compared to an average of 13 minutes in 13 control animals. However, the increase in the clotting time of the treated group was due largely to the response of 4 of the 12 animals. The others did not show significant change. The authors state, "It is suggested, but not established by experiments in dogs, that intravascular clotting may be prolonged by the previous administration of the dicoumarin in moderate dosage."

Holden *et al.*[67], studying a series of more than 50 dogs, used thrombin or trypsin to produce clotting. They found some inhibition of thrombin-induced clotting at prothrombin levels below 35%. Prothrombin levels below 15% were required to inhibit trypsin-induced thrombosis. Examination of their Fig. 2 reveals that even at prothrombin percentages below 20, there was a 24% incidence of thrombin-induced clots, and a 50% incidence of trypsin-induced clots at prothrombin percentages below 15. Although suggestive, this study, too, is not conclusive. Since Moss, Schafer and Kirby[93], experimenting on 32 dogs, produced thrombosis within a sterile glass cannula, their study is, to an extent, *in vitro*. They found some prolongation of "thrombosis time" at prothrombin levels of 40% or lower. Their results are also suggestive.

Thill *et al.*[138], in a series of 30 dogs, used monolate to produce thrombi. The 15 treated dogs received Dicumarol,

5 mg. per kg. orally, an amount equivalent to therapeutic usage. The incidence of thrombi in the control animals was 56.6%, while in the treated group it was reduced to 20%. These studies, taken together, would certainly constitute strong evidence for the anticoagulant action of therapeutic doses of Dicumarol. However, there are equally convincing studies which do not show such an action.

Rogers, Barrett and Lam[115] studied a series of 77 dogs, traumatizing veins to produce thrombi. They found no significant change in the incidence of thrombi unless prothrombin levels were less than 3%. At such levels, hemorrhagic complications occurred in all the animals.

Wessler has reported some studies of considerable importance utilizing methods of producing thrombosis which seem far more physiological than those employed in the earlier studies[147]. The isolated venous segment employed in his experiments consists, in effect, of a container lined throughout with normal venous endothelium, without the addition of any foreign substances. The blood coagulates after a considerable period of stasis. The ideal nature of this preparation lends great weight to studies performed upon it. Wessler found that although the degree of hypoprothrombinemia in the 18 dogs treated with Dicumarol was in excess of that obtained therapeutically in man, *in vivo* clotting in the isolated venous segment was not significantly retarded except in one animal whose prothrombin activity was so low that the clotting time was prolonged 3 hours. In contrast, heparin in therapeutic doses showed excellent protection in 10 of 11 dogs. It was also noted that there was no evidence that Dicumarol had even potentiated the clot-retarding effect of heparin. Although the author is quite conservative in his conclusions, stating, ". . . the anticoagulant effect of heparin was found to be superior to that of Dicumarol," the data fail to show any significant anticoagulant effect of Dicumarol, except in the one case mentioned above[148].

Wessler[149] also studied the effects of Dicumarol and heparin on S.P.C.A. (Convertin)-induced thrombosis. Dicumarol was administered to 10 dogs in doses sufficient to lower the prothrombin activity to 2% of normal or below. In only one of the 10 dogs was S.P.C.A.-induced thrombosis prevented. In this animal, clotting time had been tripled. In striking contrast heparin, in amounts sufficient to double the clotting time, prevented S.P.C.A.-induced clotting in all of the 10 dogs studied. As Wessler points out, ". . . these observations do not preclude the possibility that Dicumarol retards intravascular thrombosis." Nevertheless it is clear that the work on animals has failed to demonstrate conclusively, beyond doubt, that Dicumarol in clinically safe dosages has any significant anticoagulant action.

On the other hand, Dicumarol has been used extensively in an attempt to combat postoperative thromboembolic phenomena. Thus, it is pertinent to examine the experience of the surgeons with this drug to see if there is conclusive evidence that it acts as an anticoagulant under the conditions of clinical usage.

DICUMAROL IN THROMBOEMBOLISM. There have been many favorable reports on the prevention or treatment of postoperative thrombophlebitis[1-5,7,9-13,15,18,19,21,23,31,35,46,47,50,57,65,77,79,80,82,88a,91,94,105,106,111,112,129,133,134,137,140,141,150,163,166]. Unfortunately, none is completely convincing. Most of the studies compared the incidence of postoperative thromboembolism during a period of years when Dicumarol was adminis-

tered to the experience in previous years before the advent of this drug. However, as recognized by some of the observers, there were many other changes which also occurred during this period. Some of the factors other than Dicumarol therapy which may have influenced the incidence of thromboembolism are: the advent of early ambulation, antibiotics, better attention to fluid and ion balance, improved surgical techniques, and the growth of voluntary hospitalization insurance with a resulting improvement in general patient care. Furthermore, there is the important point that in many of the reported series, heparin was administered until the prothrombin percentage had fallen to the desired level. It is conceivable that any favorable results in such cases might have come, not from the Dicumarol, but from the heparin which was given during the most critical period in the genesis of the thrombus. Even thromboembolic phenomena manifesting themselves weeks postoperatively may have been initiated during the 48-hour period following the operation. It would be of great interest and importance to have this question answered experimentally.

It may be argued that since these considerations are largely theoretical, they should not be given much weight in view of the clinical impression of many surgeons that Dicumarol is an effective, useful anticoagulant. On the other hand, it is also necessary to consider the fact that several physicians have formed the clinical impression that Dicumarol is unsatisfactory for clinical use[6,33,34,36,38,83]. It has even been suggested[38] that small doses increase the clotting tendency. A recent review of the problem of thromboembolism from the surgical standpoint has pointed out how difficult it is to reach firm conclusions concerning the prophylactic and therapeutic usefulness of anticoagulants on the basis of clinical observations[36a]. This review also points out certain puzzling features in the earlier reports of the effectiveness of anticoagulant therapy.

Clearly, there is a good deal of controversy among the surgeons as to the value of Dicumarol. Surgical experience cannot, therefore, be given as conclusive proof of an effective anticoagulant action of clinically safe doses of Dicumarol.

Thus, in undertaking an analysis of the studies on Dicumarol effects in myocardial infarction, it is not justifiable to assume that Dicumarol as given is necessarily an anticoagulant. On the other hand, the absence of conclusive evidence of its anticoagulant action in safe dosages does not necessarily impair the validity of a clinical test. However, it may affect the interpretation of the results, directing our attention to different actions of the drug which may have modified the mortality rate.

DICUMAROL IN MYOCARDIAL INFARCTION. Before undertaking an analysis of the studies made on Dicumarol therapy of myocardial infarction, it would be well to consider the type of evidence which is likely to be convincing. In this disease, mortality and complication rates vary widely in different series. Therefore, alternate selection of patients is important. However, the alternate case method, even if rigidly adhered to, is not enough to insure accurate results. Even with so-called objective measurements the subconscious bias of the investigator may affect the answer if he knows which patient was treated and which one wasn't[28]. This is especially true in the diagnosis of thromboembolic phenomena where the criteria are sometimes not clear-cut. As Gold[27] has pointed out, a physician seeing a patient with a few rales at the bases and a vague shadow in the chest roentgenogram may be influenced

in his decision as to whether or not the patient had a pulmonary embolus by the knowledge that the patient did or did not receive an anticoagulant. On the other hand, it may be that enough patients have unequivocal signs of thromboembolism to provide convincing evidence. It may be argued that since all the studies dealt largely with death rates, the factor of subconscious bias is unimportant, inasmuch as survival and death are clear-cut end points with no possibility of confusion or distortion. This argument is correct so far as it goes, but may overlook important factors. Treated patients in any study are likely to receive extra attention from all medical personnel coming in contact with them during hospitalization. This extra attention may tip the balance favorably in some patients. Furman *et al.*[55] express similar views: "How much benefit accrues to the patient who is part of the study of any therapeutic agent, by reason of the extra interest and attention paid him, and how much better would be the outlook for the control subject were he to be favored with as much attention?"

A related problem is the psychological effect on a patient of the knowledge that he is or is not receiving a new, presumably useful treatment for a potentially fatal disease. The psychologic status of the patient is important generally; in diseases such as acute myocardial infarction, it may well decide the outcome in some cases. Even the clotting tendencies of the patient's blood may be related to emotional factors. Cannon and Mendenhall[25] showed many years ago in cats that emotional changes produce profound changes in blood clotting. This has also been demonstrated in humans by several investigators. De Takats[39] stated that patients' fear of thrombosis may actually contribute to its occurrence. Schneider[125] used the siliconized tube method of measuring clotting time and found that within relatively short periods highly significant changes in clotting time were observed in patients subjected to stressful interviews. In describing the results of his studies he states, "Patients with recurrent thrombophlebitis reacted to stressful interviews with striking shortening of the clotting time and moderate increase in blood viscosity. Nonstressful interviews failed to elicit such a response." In studying the histories of patients with recurrent thrombophlebitis, he noted that the attacks of thrombophlebitis in the past were temporally correlated with sustained periods of emotional disturbance characterized by fear, anxiety, and anger. Schneider and Zangari[126] report that ". . . the emotional states of anxiety, fear, anger and hostility were followed by shortening of clotting time."

Macht[87] studied the effects of emotions on the clotting time of blood donors. He reports that the clotting time of calm persons ranged from 8 to 12 minutes, that of apprehensive donors ranged from 4 to 5 minutes, while that of highly nervous donors was shortened to 1 to 3 minutes. These findings are of particular interest, since they were observed in a glass tube, and as pointed out before, Dicumarol in clinically safe doses is unable to modify glass tube clotting time. Others[49,131,143,152] have also commented on the importance of emotional factors.

In the light of these studies on the influence of emotions on blood clotting time, it is appropriate to consider the psychologic status of patients in studies which did not employ the double-blind technique. Most patients with myocardial infarction experience fear and anxiety, sometimes of great intensity and duration. However, the knowledge that he is receiving a new, potentially lifesaving drug in which his physician

has great faith may well relieve much of his fear and anxiety, and thus reduce the coagulability of his blood. In some cases the patient or his family may find out directly that a drug in which his physician has confidence is being administered. In other cases such information may be imparted indirectly and unconsciously by the physician's manner, attitudes, and the inflections of his voice. The control patients, however, would not receive the benefit of such impressive reassurance, and in them the clotting tendency might, as a result, continue to be elevated. Therefore, the failure to control adequately the subconscious bias of the investigator and the emotional status of the patient might result in serious errors. The only type of experiment which appears likely to be completely convincing is one which employs the double-blind technique, in which neither the patient nor the physicians in contact with the patient know whether a drug or a placebo has been administered. This experimental design effectively avoids error due to subconscious bias or to the patient's emotional response. Gold[27] has pointed out that the absence of a double-blind method for gathering data may weaken the argument for Dicumarol.

In surveying the extensive literature on the effects of Dicumarol in myocardial infarction, no study has been found which incorporates the essential double-blind feature[22,26,31a,55,56,59-62,64,66,68,69,74,75,86,90,95-98,100-104,110,111,114,124,132,139,153,157,159-162,164].

It appears, then, that none of the evidence is completely convincing, although it might be considered suggestive. Many studies were performed on such small series of patients that the results could not be statistically significant even if the experimental design were otherwise unassailable. In other studies comparable controls were not used; the treated cases were compared to untreated cases of previous years. Nevertheless there have been a substantial number of studies, performed with concurrent controls, in which the evidence suggests that Dicumarol does lower the mortality rate[26,68,86,104,110,124,132,139,162].

The most extensive study thus far performed on the effects of Dicumarol in myocardial infarction is that of the American Heart Association Committee under the chairmanship of Wright[162]. Since this study constitutes the major evidence favoring the use of Dicumarol in myocardial infarction, it is pertinent to consider it in some detail. Parenthetically, it may be added that this extensive work also provides a great deal of important information about other aspects of myocardial infarction. Preliminary reports were published in 1948[160,161], and the final report in 1954[162]. It has been the subject of favorable editorial comment in the J.A.M.A.[44a]. This study, conducted in 16 hospitals cooperatively, involved more than 1,000 patients and included painstaking statistical analyses of the results. All the data were entered on standardized forms and transmitted to the central office for compilation and interpretation. All hospitals were expected to follow the plan of treatment outlined by the central group. Patients were to be placed into "treated" or "control" groups depending on the date of admission. Those admitted on odd-numbered days were to be given anticoagulants, while those admitted on even-numbered days were not.

Ward, semi-private and private cases were included in the study, and the results were analyzed both for the entire group, and for the various subdivisions. Necropsy findings were also presented in detail. Heparin was administered to 15.4% of the patients[162, p 23], for the first day or two, until the

desired effects of Dicumarol on the prothrombin time were obtained.

The results showed a remarkable similarity in the constitution of the control and treated groups in respect to many factors such as age, sex, and severity of illness. This suggests that the two groups were comparable in all important respects, except the administration of Dicumarol. The mortality rate in the control group was 23.4%, in the treated group only 16.0%[162, p. 307], a highly significant decrease. In the control group, 26.0% of the patients developed thromboembolic complications, while in the treated group, only 10.9%[162, p. 196] did so, an impressive difference. Even when the results are broken down by various patient categories, there appears to be a definite benefit from Dicumarol. For example, private treated cases had lower mortality and complication rates than private control cases[162, pp. 239,325,578]. Wright *et al.*[162, p. 201] point out that even when the data from individual hospitals are examined, the incidence of thromboembolism diagnosed clinically is significantly lower in the treated group.

Despite the impressiveness of these findings, however, there are some aspects of this study which may modify our interpretation of the results. Although the initial plan called for the alternate case method, a substantial proportion of the patients were treated out of turn[162, p. 9]. When an alternate case method is not strictly adhered to, questions may be raised concerning the validity of the results. One of the investigators[28] associated with this study expressed some concern over the fact that the design for treated and untreated cases in the 16 hospitals was not always adhered to. Here was a new drug supposed to be helpful for a disease which carried a high mortality. The word soon got around among the patients in the hospitals and among the families that certain patients were receiving the drug and others were not. In many instances great pressure was brought to bear to see that certain cases would receive it. It is clear that the committee was aware of the possible source of error in patient selection, and endeavored to apply statistical corrections.

Another feature of importance is the relationship of the private physician and house staff to the patient and to the Committee. It may be deduced that the private physicians or, in ward cases, the house staff, were the ones in direct daily contact with the patient, and their attitudes and beliefs about the new treatment were transmitted to the patient or his family in one fashion or another. Also, the many details of general treatment were apparently left entirely in their hands. It is not unreasonable to ask whether some of these doctors spent more time with their treated patients than with the controls. The question whether increased attention and nonspecific treatment can favorably influence mortality rates in myocardial infarction may be answerable from the Committee's report. The mortality rate in the treated ward cases was 19.0%, while the mortality in the control private cases was 20.1%[162, p. 578]. Since these rates are almost identical, one might deduce that changing a patient from ward to private status is as effective as anticoagulant therapy in reducing mortality. It is not inconceivable, therefore, that devoting still more time and attention to patients may reduce their mortality further. Wright *et al.* are aware of this factor[162, p. 324] but apparently do not consider it of sufficient importance to affect seriously the validity of their conclusions. They point out that even when ward and private patients are considered separately, the complication and mortality rates are significantly lowered in the

treated patients[162, pp. 239,325]. However, the question which remains to be answered is whether treated private patients received more individual attention from all medical and nursing personnel than did control private patients, and whether treated ward patients received more attention than control ward patients. If so, it may be that the difference in amount of individual attention, rather than the specific medication, was responsible for some of the beneficial effects. On the other hand, it is also possible that in Wright's series, the ward patients may have been in poorer condition at the beginning of anticoagulant therapy than the private patients.

There is one curious aspect to the difference in mortality rates between ward and private patients. Appendix Table 33 of the American Heart Association report[162] indicates that of the 16 participating hospitals, 7 involved ward services only. If the mortality rates are calculated for these 7 hospitals only (Appendix Table 37), they are found to be almost identical: 21.5% for the control and 21.2% for the treated. It is possible that in some of these hospitals, the more seriously ill patients were admitted more often on odd-numbered days so that they might receive Dicumarol, thus prejudicing the results against Dicumarol. Unfortunately, since a double-blind procedure was not followed, it is not possible to evaluate the significance of these observations.

The necropsy reports support the thesis that the treated patients had less thromboembolic complications. Of the control patients examined at necropsy, 44% had extracardiac thromboembolic complications, while only 28% of the treated patients had them[162, p. 413]. There were 125 thromboembolic complications per 100 cases among the untreated, and 45 per 100 cases among the treated patients[162, p. 415]. However, there seems to be an increase in the incidence of hemopericardium and cardiac rupture with Dicumarol[162 pp. 422, 426]. In the necropsy sample, 12% of the treated cases had hemopericardium, compared to 2% of the control. The degree of hemopericardium varied widely, but in at least 2 cases was sufficient to cause or contribute to a fatal outcome. Wright *et al.*[162, p. 297] conclude that although anticoagulants increase the risk of hemorrhage, adequate control procedures keep the increase sufficiently slight so that the benefits of anticoagulants greatly overbalance the accompanying risk of hemorrhage.

Although there were more cases of cardiac rupture in the treated than in the control group, the total number was too small for statistical significance. Therefore, Wright *et al.*[162, p. 423] suggest that judgment as to an association between cardiac rupture and anticoagulant therapy must be suspended pending further studies. Others[63,142] have also pointed out the risks of hemopericardium and cardiac rupture from Dicumarol.

The picture is further complicated by the fact that there have been other reports indicating various degrees of disagreement with the conclusions of the American Heart Association Committee[20,40,48,51,53,54,123,152]. However, none of the adverse opinions are supported by adequately controlled double-blind studies and therefore are also not decisive. The impression gained from all reports is that although the weight of opinion seems to favor the use of Dicumarol, the question of its value is not completely settled.

Another facet of the Dicumarol problem is whether it should be administered to "good risk" patients. Wright has pointed out that no one

can predict which patient may develop a thromboembolic complication, and, therefore, advises that all patients be given the drug. He has recently re-emphasized this advice[162, p. 235] and is supported by other investigators[26,110]. In addition, many others who have not commented directly on this point are undoubtedly in agreement with Wright. There are still others who disagree and would reserve the drug for "poor risk" patients only[8,41,42,44,52,76,84,102,116-122,127,128]. This question, too, will probably have to remain open until a definitive, conclusive study is reported.

An additional aspect of the problem is the lack of agreement, even among those who report good results from Dicumarol, as to the mechanism through which such benefits occur. Wright and his coworkers[162, p. 307] report that the lowered mortality results largely from a lowered incidence of thromboembolic complications. This view is supported by the evidence of several studies. On the other hand, a number of investigators[56,61,78,86] who also report beneficial results from the drug were unable to explain them on the basis of a lowered incidence of thromboembolic phenomena. Furman *et al.*[56] state, "We could not, therefore, account for lowered mortality on the basis of prevention of peripheral or pulmonary thromboembolic phenomena." Loudon *et al.*[86] state, "Thus in the present paper there is no definite indication how anticoagulant therapy lowers the mortality rate from myocardial infarction, although it is quite clear that there is a significant reduction." Kyser[78] writes, "I firmly believe that the beneficial effect of anticoagulant therapy is the result of some other action in addition to its anticoagulating ability. Of all the reports that have been published there is no question in my mind that embolic phenomena are not the major cause of death and yet certainly in our own experience and in the experience of other workers adequate treatment with anticoagulant drugs lowers the mortality." Inasmuch as several proponents of Dicumarol therapy are unable to agree on the mechanism of Dicumarol action, the need for further studies in this field is apparent.

OTHER ACTIONS OF DICUMAROL. Related to this aspect of the problem are the reports of other actions of Dicumarol. Several investigators have commented on its pain-relieving properties in different areas of the body[7,35,96,97,163,166]. Bingham, Meyer and Pohle[16] report that therapeutic doses in dogs produce a capillary, arteriolar, and venule dilatation. Eisen *et al.*[45], Meyer[136], and H. P. Wright[154] found that it reduced the adhesiveness of blood platelets. Gilbert and Nalefski[58] suggest that it increases coronary flow. Walton and his associates[145] showed that large doses, 25 to 50 mg. per kg., produced a marked increase in the contractile force of the heart in dogs. Wolf[151] suggests a possible antipyretic property. H. P. Wright and her associates[155,156] have demonstrated that Dicumarol speeds the rate of recanalization of thrombi in rabbits. Quick[109] suggests that Dicumarol interferes with the labilization of platelets. It is possible that one of these actions, or some other as yet undescribed, may be related to the beneficial action noted in many cases of myocardial infarction. This area also requires further investigation.

DICUMAROL TOXICITY. Excessive doses of Dicumarol will, of course, cause bleeding and sometimes death. However, in clinical usage, those who have had the greatest experience with this drug[162] report that with careful attention to prothrombin levels and contraindications, Dicumarol toxicity is not great. On the other hand, there are other reports which suggest that, as

currently employed by physicians who may not be experts, Dicumarol has been responsible for many fatalities[48, 83,119]. Also, the recent recognition of the increased hazard of hemopericardium and possible hazard of cardiac rupture from Dicumarol must be considered[63,142,162]. Wright and his associates have formulated clear-cut rules for the regulation of Dicumarol dosage. If Dicumarol is used, it seems wisest to follow those recommendations carefully.

HEPARIN. The anticoagulant action of clinical doses is conclusively established. However, the usefulness of heparin alone in myocardial infarction has not yet been adequately investigated. Loewe and Eiber[85] studied heparin alone in a series of 20 patients. Their results were good, but the series was too small to be statistically significant.

MEASURES NEEDED TO SOLVE THE PROBLEM. It is apparent from the evidence cited and from the survey of Russek and Zohman[119] that many physicians utilize Dicumarol routinely in cases of myocardial infarction. On the other hand, a large number apparently employ this drug only in their "poor risk" patients, and some physicians, unconvinced of its usefulness, employ it only when forced to by patient, family, or referring physician. Clearly, a substantial number remain unsatisfied with the evidence of Dicumarol's worth. This may have serious implications in terms of patient mortality. Wright[158] has pointed out that coronary thrombosis kills at least 200,000 people a year in the United States. If Dicumarol is in fact able to lower the death rate from infarction in all types of cases, the unwillingness of many physicians to follow Wright's recommendations may result in preventable deaths. On the other hand, if Dicumarol does not lower the death rate in all types of cases, some patients are being treated needlessly with a potentially dangerous drug. Thus it seems important to answer definitively the questions about the value of Dicumarol.

The study by the American Heart Association Committee probably cannot be improved upon if the simple alternate case method is employed. It is, therefore, unlikely that any future studies performed in the same manner will be more convincing. Probably only a study employing a rigid double-blind procedure will be conclusive. Such a study on a statistically significant number of patients would be expensive and laborious. However, a project which may have been impossible 8 years ago may be feasible today. Similar double-blind studies have been performed on great numbers of children to evaluate preventive measures for poliomyelitis. The public knows and approves of such procedures. It may be practical now to perform a suitably designed double-blind study in myocardial infarction. It may be argued that although such a study is academically ideal, it is too difficult to accomplish practically, since the physician in charge will not know what the patient is receiving, and since the dosage must be varied daily, and bleeding or thrombosis may occur. However, Gold, and Quick[28] have suggested some approaches which seem practical and which deserve a trial. The importance of this question in terms of patients' lives warrants considerable expenditure of time and money.

Another aspect of the Dicumarol problem which deserves immediate attention is a clear demonstration of the basic pharmacology of this drug. Many of the current clinical problems can be traced to the absence of basic pharmacologic information about Dicumarol in clinical doses. It has been pointed out that in the view of some workers there is no conclusive evidence that it is an effective anticoagulant in safe doses.

The other possible actions which have been suggested[7,16,35,40,45,58,61,88,96,97,136,145,146,151,154,156,163,166] should also be carefully explored. Without a thorough understanding of the basic pharmacology of a drug it is not likely to be used clinically to best advantage.

It also seems advisable to investigate the value of heparin alone for varying periods of time in myocardial infarction[116]. If, as has been suggested, Dicumarol lowers the mortality rate through some mechanism other than an anticoagulant action, it may be that heparin will further reduce mortality.

Finally, the effect of the patient's emotional state on the prognosis in myocardial infarction deserves re-evaluation.

Conclusions. Extensive and careful investigation of the value of anticoagulants in the treatment of myocardial infarction has been carried out. While the weight of evidence suggests that they may be of value, this cannot be considered completely conclusive at this time. The physician who decides to use Dicumarol for almost all cases of myocardial infarction can find abundant evidence to justify his course. On the other hand, the physician who decides not to use this drug can also logically support his position. There is a great need for more research in this area. It is suggested that a clear and convincing demonstration that Dicumarol in clinically safe doses is an effective anticoagulant would be very helpful. It is further suggested that, although the practical difficulties involved in a double-blind study on large numbers of patients are fully appreciated, such a double-blind procedure should be utilized to obtain fully conclusive results.

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RADIOLOGY

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ANGIOCARDIOGRAPHY AND THORACIC AORTOGRAPHY IN CONGENITAL CARDIOVASCULAR LESIONS

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THE roentgenologic contrast methods for the examination of the heart have been available as practical procedures for seventeen or eighteen years. The most important application of these techniques has been in the field of congenital cardiovascular disease. The accuracy with which simple and complex anomalies may be diagnosed is often enhanced by the procedures and the success of corrective cardiovascular surgery thereby improved. The volume of literature on this subject has become too voluminous to review completely, so that only the important contributions to diagnosis will be discussed. An excellent review of the history of angiocardiography and aortography and of the development of special radiological equipment has been written by Scott[181].

Technique of Angiocardiography and Aortography. For the majority of congenital cardiac lesions, the intravenous method of angiocardiography, developed by Castellanos *et al.*[25,27,29,35,36,37,38] in children and Robb and Steinberg[170,171,172,173] in adults, is the best procedure. It has been well established by Lind *et al.*[76,138,208,209] that much more anatomical and physiological information can be obtained in these anomalies if the rapid serial film changers taking 10 to 12 films per second in two planes at right angles simultaneously are used. This type of equipment has revealed many lesions which were not visible in studies at slower speeds of 1 to 2 films per second.

It has been stated that Urokon is the best contrast medium[62] of the three substances now in common use: 70% Urokon, 70% Diodrast, and 75% Neo-Iopax. The subjective reaction to Urokon is somewhat less and it is at least as safe and perhaps safer than the other media. The dosage of contrast medium used by most authors is 1 to 1.5 cc. per kilogram body weight (up to 50 cc. for adults) with the higher

dosage employed in patients with enlarged hearts.

Although general anesthesia was at one time widely employed in angiocardiography, it is now considered entirely unnecessary. In addition it frequently increases the risk of undesired reactions in cyanotic infants and children. Pre-medication with a combination of morphine, scopolamine or Nembutal with local anesthesia for the cut-down incision is quite adequate.

The technique of selective or intracardiac angiocardiography, in which the injection is made through an intracardiac catheter was developed by Chavez *et al.*[39] and Jönsson[110]. It is useful in special cases in which exact anatomical details are desired in a localized area of the heart, for example, the infundibular and pulmonic valvular areas in pulmonic stenosis[112,113]. It is also valuable in adults to inject through a catheter in the pulmonary artery for better visualization of the left chambers[201]. The injection of 1 to 1.2 cc. of 70% contrast medium per kilogram body weight[113] is usually made with a pressure apparatus in 3 to 4 seconds.

Many different methods of thoracic aortography have been described but only three are widely used. The first or "counter-current" method developed by Castellanos[30,31,32] is still the most suitable method for infants and young children. An injection of 1 cc. of 30% contrast medium per kilogram body weight is made forcibly into the exposed brachial, ulnar or radial arteries to opacify the thoracic aorta by retrograde flow. In adults, the catheter method developed by Jönsson *et al.*[15-17] and Radner[167,168] is satisfactory. The catheter is inserted through the exposed radial artery and the catheter tip is placed either in the middle of the ascending aorta or in the descending aorta. Thirty to 50 cc. of contrast medium are injected, usually with pressure apparatus in 3 or 4 seconds. In catheter aortograms, 70% contrast media may be used but 50% concentration is safer[16]. The percutaneous femoral artery puncture method with insertion of polyethyelene tubing, as developed by Peirce[159] is satisfactory for some anomalies. It avoids a skin incision and arterial suturing, but is unsuitable for coarctation of the aorta. Thoracic aortography has been used chiefly in coarctation of the aorta, patent ductus arteriosus, aortic hypoplasia, aorticopulmonary septal defect and persistent truncus arteriosus[125].

The Reactions and Risks of Angiocardiography. THE USUAL REACTION. There is marked individual variation in the tolerance of patients to the rapid injection of 70% contrast material. Many symptoms have been described but most last only for a few minutes before regressing. These include a generalized wave of intense heat or burning, palpitation, headache, coughing[177], momentary irregularity in respiration[24, 47,121], flushing of the skin[33,127,197], venous spasm, nausea and vomiting, urticaria, rhinitis, lacrimation, salivation, and syncope. Patients who have been under general anesthetic may have attacks of sneezing on recovery[47]. There is also a transient increased cyanosis in cyanotic individuals. The changes in the pulse rate are quite variable, but there is usually an initial period of stimulation[89] with an increase in heart rate ranging from 4 to 70 beats per minute, and an average of 27[105]. Following this there is a gradual slowing of the heart rate with return to normal in 3 to 4 minutes. Often in the first thirty seconds, there is also stimulation of the rate and depth of respiration; occasionally, however, respiration is decreased[89]. Immediately following injection, there is a rise in venous pressure to as high as 300 mm. mercury

and in the first few seconds there is a slight rise in the systolic and diastolic pressure[89]. In about 5 to 20 seconds, there is a drop of both the systolic and diastolic pressures[106] sometimes by as much as 30 to 60 mm. mercury[47]; the blood pressure usually returns to normal in about four minutes[89]. Control injections of saline cause no such changes in blood pressure[106]. Gordon *et al.*[89] believe that the fall in the blood pressure is due to a direct vasodilating effect of contrast material on the vascular smooth muscle, and that the later bradycardia is due to a direct depressant action of the medium on the myocardium.

Thrombosis of the injected vein commonly occurs, even when the vessel is not ligated. In one series[62], venous thrombosis occurred in 48% of cases after one injection, 76% after two injections and 100% after three injections.

ELECTROCARDIOGRAPHIC CHANGES. Some electrocardiographic abnormality was noted by Reynolds[169] in 60% of 73 angiocardiograms done mostly in patients with cyanotic heart disease. Twenty-five per cent of the studies had abnormal rhythms; 25% had conduction defects and one-third of the studies had S–T segment changes, the changes in the P and T waves being insignificant. Cases of severe reaction to the contrast medium had depressed conduction and S–T segment deviation. In three fatalities as a result of the injection, the initial change was an ectopic pacemaker; one of the fatalities ended with ventricular flutter and fibrillation. Horger, Dotter, and Steinberg[105] observed changes in the T–waves and R–T segments beginning 10 to 16 seconds after injection and varied from slight decrease in amplitude of the T–waves to flattening or inversion. Auricular or ventricular extrasystoles were also noted in about half the patients. According to Zinn[216], the extrasystoles usually appear 2 to 3 minutes after injection and may take as long as 10 to 25 minutes to completely disappear. Short bursts of ventricular tachycardia due to alternating foci of ventricular irritability have been noted in one case[216]. Partial heart block has been initiated by injection in one case at The Johns Hopkins Hospital. The early changes in the S–T segment suggest the production of a transient myocardial anoxia[105,216] resembling the changes of acute coronary insufficiency; either these changes or the cardiac irregularities may be important factors in angiocardiographic deaths. In electrocardiograms performed in retrograde aortography, the changes are less marked than in angiocardiography; the S–T segment changes are absent and the extrasystoles quite transient[216].

SEVERE NON-FATAL REACTIONS. In an attempt to prevent severe reactions, a few contraindications to angiocardiography have been enumerated[181]. These include allergic diseases and allergy to the contrast medium; liver and renal disease; bundle branch block. Preliminary sensitivity tests have not proved very useful in predicting severe reactions. Intraocular, intradermal, or intravenous tests with 0.1 cc. of contrast medium in infants and 1.0 cc. in adults have been used.

In The Johns Hopkins Hospital series of 782 angiocardiograms, there were 17 severe reactions, an incidence of 2%. The incidence with 70% Diodrast was 2.4% and with 70% Urokon 1.6%. The severity of the usual reaction was less and the incidence of the severe reactions was somewhat reduced when Urokon was used instead of Diodrast. All the reactions except one were over in the first thirty minutes; in the one exception, the reaction occurred after several hours in a patient with definite pre-existing renal disease. The com-

mon manifestations were severe vomiting, severe coughing, headache, generalized flushing, excessive palpitation, edema of the eyelids or face, urticaria and itching, and tetany. One case had a severe asthmatic attack initiated by the injection. In Reynolds'[169] series of 73 cases in cyanotic congenital heart disease, there were 3 severe reactions (4%).

A case of air embolism in an adult angiocardiogram performed in the sitting position was reported[67]. Air was aspirated through a catheter in a cervical vein; the patient collapsed with generalized convulsions, stertorous breathing and bradycardia, but recovered in a few minutes. Films showed air trapped in the pulmonary artery with an air-Diodrast level.

Several measures have been carried out in the treatment of severe reactions. The most beneficial form of therapy appears to be oxygen by mask, promptly administered; 25% Coramine[37], aminophylline intravenously, and intravenous or intracardiac Adrenalin have been used. Adrenalin, however, may be contraindicated[57] because of its vasoconstrictor effect on the pulmonary vascular tree. In a controlled study of intravenous urograms, Sanström[178] found that the incidence or severity of reactions was not reduced by antihistamine drugs; if anything, the incidence of the reactions was somewhat increased. This author stated that there is no evidence to suggest that reactions to contrast media are allergic or true hypersensitivity reactions.

The largest series of angiocardiographic deaths was reported by Dotter and Jackson[56] in 1950. They received 1,378 replies to a questionnaire sent to hospitals in the United States and Canada and from a smaller group of centers in Britain and Sweden. From a total of 6,824 angiocardiograms, 26 deaths were collected, resulting in a mortality rate of 0.38%. The mortality rate was approximately one hundred times that of intravenous pyelography. It was well established that the risk of angiocardiography is much lower in adults with acquired cardiovascular lesions than in infants and children with congenital lesions. Hence, the mortality rate figures were much higher in Britain (1.7%) than in the combined U.S.A. and Canada group (0.3%) because in the former, the procedure was largely confined to children with congenital heart disease. In one combined series of 2,500 angiocardiograms in adults, no mortality occurred[56]. Seventeen of the 23 deaths collected by Dotter and Jackson were children under 8 years of age with congenital

TABLE 1.—ANGIOCARDIOGRAPHIC DEATHS

Authors	*No. of Angiocardiograms*	*No. of Deaths*	*Mortality Rate*
Campbell & Hills[21]	50	2	4 %
Carnegie[23]	172	4	2.3 %
De Groot[47]	50	1	2 %
Dimond & Gonlubol[54]	100	2	2 %
Dotter & Jackson[56]	6,824	26	.38%
(U.S. & Canada	5,961	18	.3 %
(Great Britain	413	7	1.7 %
(Sweden	450	1	.2 %
Goodwin *et al.*[87]	118	2	1.7 %
Reynolds[169]	73	1	1.4 %
Selen & Wiklund[177]	100	1	1 %
The Johns Hopkins Hospital	782	8	1 %

lesions: 14 were cyanotic. Thus the risk of angiocardiography is higher in the patients who need the study most.

Death occurred in the first ten minutes after injection in about one-third of the cases, but other patients died up to 3 days after the procedure. Delayed deaths more than 6 hours after injection are unusual, but occur in patients with renal damage[56,79]. Urinalysis should always be done prior to angiocardiography; if the procedure must be done in cases with renal damage, the dosage of the medium should be kept low and the patient should be well hydrated after the procedure.

Increasing cyanosis, vomiting, loss of consciousness, convulsions are the common symptoms prior to death. Most deaths appear to be due to respiratory arrest, but a few are due to sudden cardiac arrest or circulatory collapse. Postmortem examination often sheds no light on the cause of death; pulmonary congestion, pulmonary edema and aspiration pneumonia are the common findings. The available evidence suggests that the pulmonary vessels are the most vulnerable structures to the direct irritation of the contrast medium[56]; this danger appears to be significantly greater when there is marked slowing of the pulmonary circulation. Fifteen of the 23 Dotter-Jackson fatalities had some form of pulmonary stenosis. Sixteen of the cases had a general anesthetic. The sensitivity tests were negative in 19 of the 23 cases and were of no value in foretelling the catastrophes.

The majority of authors believe that the risk is greater when more than one injection is given. Two injections may be justified if they are given at least one hour apart; three injections should never be given at one time. Goodwin *et al.*[87] believe that deaths are most often due to cerebral catastrophes: one of their cases died of subdural hematoma, and another developed a further paralysis following the procedure and eventually died in 2 weeks. If this hypothesis were entirely true, the risk of angiocardiography in transposition would be considerably greater than in other anomalies because of the relatively dense contrast substance which reaches the cerebral vessels as a result of the early filling of the aorta; no increased risk with transposition, however, has been noted[43,47].

At The Johns Hopkins Hospital, the first 5 angiocardiographic deaths have been previously reported by Morgan[152], with a mortality rate of 1% using 70% Diodrast. Since early 1952, the procedure has been performed on 245 patients using 70% Urokon in place of Diodrast with 3 deaths resulting (1.2%). The mortality rate, therefore, has not been lowered thus far by Urokon; furthermore, the majority of patients in the Urokon series received only a single injection of the medium.

In The Johns Hopkins series, primary pulmonary hypertension and pulmonic stenosis appear to carry more risk than other lesions. In a total series of 782 angiocardiograms, none of the deaths occurred in 100 acquired lesions in adults. All 8 deaths occurred in the group of 682 angiocardiograms which includes congenital cardiovascular lesions, chiefly in children, plus cases of primary pulmonary hypertension. Of the 8 deaths, three had primary pulmonary hypertension with pulmonary arteriosclerosis, two had isolated pulmonic stenosis, and three had transposition of the great vessels (two of these had pulmonic stenosis and one had a Taussig-Bing transposition with marked pulmonary arteriosclerosis). Three of the cases died in the first hour, and the others died between 4 and 24 hours. The first death in the series was given three injections of Diodrast; since then, never more than two injec-

tions have been given on the same day. Two of the fatalities had two injections; three had only one injection; two of the fatal cases[135] died following the test dose of 1 cc. 70% Diodrast. All of the fatalities excepting the two from the test dose had negative intravenous sensitivity tests. There has been one other fatality from a test dose of 1 cc. 70% contrast medium reported[45].

Reactions and Risks of Selective Angiocardiography. When injection is made through an intracardiac catheter, the risks are somewhat greater than in the intravenous method[125], because there is a combination of the risks of catheterization and angiocardiography. As a result of the intracardiac injection, there are abrupt changes in pressure and a greater irritative effect of the contrast medium on the endocardium because it is relatively undiluted with blood.

REACTIONS. Arrhythmias immediately after the injection of the contrast substance occur in about one-third of the cases[201]. Ventricular extrasystoles, auricular fibrillation, short runs of nodal rhythm and transient cardiac standstill have been noted[201]. Arrhythmias may be frequently produced merely by rapidly injecting saline. The interventricular septum and tricuspid valvular area are relatively sensitive to the tip of the catheter, and the right atrium relatively insensitive. The immediate reaction to the injection (that is, intense feeling of warmth, headache, nausea, and vomiting) is more severe than when intravenous angiocardiography is performed. In a case of pulmonary arteriovenous aneurysm[176] an injection of 65 cc. 70% Diodrast through a catheter with the tip in the main pulmonary artery caused hemoptysis and apnea for 2 or 3 minutes following injection.

DEATHS. No deaths or serious reactions were reported by Jönsson[118] in 100 cases, and by Kjellberg[131] in 150 cases in children. Chavez *et al.*[39] reported one death in over 400 cases. Sutton[201] had one death in 36 cases due to the catheterization.

At The Johns Hopkins Hospital, 2 deaths following selective angiocardiography have occurred. The first, a case of multiple pulmonary arteriovenous aneurysms, was reported by Sisson, Murphy and Newman[183]. With the catheter tip in the right atrium 35 cc. of 70% Diodrast were injected; death occurred in 25 minutes due to acute pulmonary edema. The second death occurred in a patient with rheumatic mitral stenosis with minimal insufficiency. Intravenous angiocardiography was tolerated well, but was unsatisfactory for demonstration of the left chambers because of the extremely slow circulation time. Forty cubic centimeters of 70% Urokon were injected by pressure apparatus in 3 seconds through a catheter in the left pulmonary artery. The immediate reaction to the injection was intense and prolonged with marked discomfort in the entire upper trunk; a shock-like state developed with rapid thready pulse, extreme pallor and prostration. A chest film in a few hours later showed massive consolidation in the left lung. In spite of resuscitative efforts, the patient's condition steadily deteriorated and death occurred some 40 hours following the injection. At necropsy a massive infarct of the left lung was found with a thrombus in the left pulmonary artery.

Reactions and Risks of Thoracic Aortography. In general, the risks of thoracic aortography are somewhat greater than in intravenous angiocardiography[184], but the immediate generalized reaction is milder[178]. The usual subjective sensation is a feeling of warmth in the head[15]. Following injection, there is usually bradycardia for

a few seconds, followed by tachycardia lasting for about one minute[11].

At least 7 deaths have occurred from thoracic aortography[31,40,64,82,184,187]. The great majority of deaths and severe reactions are cerebral complications due to excessive quantities of contrast medium reaching the brain through the carotid arteries. They are, therefore, very similar to those encountered in cerebral arteriography. In the counter-current method of aortography used in infants and young children, deaths have occurred from the use of 70% contrast media[31,40,82]. Satisfactory studies of this type can be obtained using the 30 or 35% contrast media so that the use of more concentrated media is not justified. In the catheter aortograms in adults, the 70% media can probably be safely used, provided the catheter tip is not in close proximity to the innominate or left common carotid arteries. Peirce[160] reported two cases of temporary hemiplegia from the use of 70% Diodrast in catheter aortography which appeared in half to one hour following injection with recovery in one and four days; one of the cases had temporary aphasia. Chou[40] reported two cerebral complications in adults in whom the counter-current method was used. He injected 30 and 45 cc. of 70% Diodrast and in one case spastic contractions of the upper extremities, aphasia and convulsions developed and death occurred in 8 hours. In the other case, there was no reaction for several minutes, but the patient then became unresponsive and a flaccid paralysis developed in both arms which lasted several weeks.

At The Johns Hopkins Hospital, 2 deaths from thoracic aortography have occurred and were reported by Sloan[184]. These occurred in a series of 90 thoracic aortograms, 70 of which were in suspected congenital lesions and 20 in suspected acquired lesions. This constitutes a mortality rate of 2%. The first fatality occurred in an adult female with pseudotruncus arteriosus; the tip of the catheter was inadvertently placed in the left common carotid artery and 22 cc. of 70% Diodrast were injected manually; all the contrast substance ascended into the cerebral vessels; immediate convulsions, marked cyanosis and death in 4 hours resulted. At postmortem examination the brain showed multiple small acute hemorrhagic foci. The second fatality occurred in a 4-month-old infant with the catheter inserted through a carotid artery; during fluoroscopy there was considerable hemorrhaging at the site of the catheter insertion, the infant went into shock and died in 4 hours. Two non-fatal but severe reactions also occurred in this series, an incidence of 2%. In one infant with complete coarctation using the counter-current method of aortography, 70% Urokon was injected by mistake instead of 30%; severe cyanosis and convulsions resulted but complete recovery occurred in several hours. In one catheter thoracic aortogram in an adult with coarctation and patent ductus arteriosus, injection of 40 cc. of 70% Diodrast resulted in temporary oliguria, bilateral flank pain, fever, and albuminuria. The symptoms disappeared in a few days. In this case, apparently temporary renal damage occurred as a result of the injection, similar to that more commonly seen as a complication of abdominal aortography.

In the percutaneous retrograde method of aortography, about 10% of patients will develop small hematomas at the site of puncture[159]; one case of small extraperitoneal hematoma and one case of arteriovenous fistula at the site of puncture also occurred[159].

Clinical Application. The contrast radiological methods play a subordinate role in the diagnosis of congenital

cardiovascular lesions and are used only after patients have been investigated by clinical methods and cardiac catheterization. The procedures have been performed in from 15%[125] to 50%[181] of patients in congenital cardiovascular clinics.

The greatest indication for angiography occurs in problem cases in which the diagnosis has not been made or is not very certain after clinical investigation and cardiac catheterization. Secondly, the contrast methods have been used when the patient's diagnosis has been established but when exact anatomical details are required prior to surgery, as, for example, in coarctation of the aorta. Thirdly, when the diagnosis is reasonably certain clinically and the lesion is a hopeless non-surgical one, angiography may give confirmatory evidence of the nature of the lesion and assurance that a correctible lesion has not been missed. In general, angiography has proven more useful in cyanotic than in non-cyanotic anomalies, but there are several exceptions to this rule. In cases with multiple shunts, angiocardiography is reliable in the demonstration of the most proximal shunt only; the method does not usually demonstrate valvular lesions directly, and it is especially poor for valvular lesions of the left heart. Even after all available diagnostic methods including angiography have been performed, the percentage of errors in complex and multiple anomalies is still quite high. The angiographic signs of the specific anomalies which have been described in the literature will be enumerated and briefly discussed.

Tetralogy of Fallot. 1) SIMULTANEOUS FILLING OF THE AORTA AND PULMONARY ARTERY FROM THE RIGHT VENTRICLE IN THE EARLIER FILMS DUE TO OVERRIDING OF THE AORTA. The shunting of the contrast medium from the right ventricle to the aorta can be demonstrated in all cases[87]. The actual abnormal dextro-position of the aorta often fails to show in the A.P. views[82], but in the left oblique view the origin of the aorta overriding the ventricular septum can be seen. In lateral films, the abnormal anterior position of the ascending aorta can be detected, usually midway between its normal position and that of transposition of the aorta; the origin of the pulmonary artery is still anterior to that of the aorta. The degree of overriding can be accurately evaluated; the denser the aortic filling from the right ventricle and the poorer the filling from the left ventricle in the later films, the greater the degree of overriding. The amount of overriding is of prime importance in prognosis, for when severe there is a "functional stenosis" of the left ventricle; after the creation of an artificial ductus arteriosus, this may result in marked left heart enlargement[41].

2) THE DEMONSTRATION OF THE PULMONIC STENOSIS. In most cases, the stenosis involves the infundibulum of the right ventricle, but in a few cases it is valvular, and in some there is a combined valvular and infundibular stenosis. In A.P. views, the direct demonstration of the stenotic area and estimation of its severity can be obtained in only about 20% of cases[87], because it is often obscured by early filling of the aortic arch or left ventricle, or by a left superior vena cava[41]. When the area is well visualized, a definite infundibular chamber is sometimes demonstrated[87]. In lateral views, the stenotic site is often obscured by the enlarged right auricular appendage[112]. On isolated films, the normal periodic contractions of the infundibular region may be mistaken for infundibular stenosis; it is, therefore, essential to demonstrate the constriction on more than one film[41]. Several authors [102,142] have

shown that the infundibular stenosis is best demonstrated in the right oblique view. By rapid serial angiocardiography in this view, Hilario, Lind and Wegelius[102] showed the morphology of the stenotic area in 70% of their cases. Changes in the infundibulum with the phases of the cardiac cycle were also demonstrated; the stenosis became more pronounced in systole. The infundibulum is usually conical in shape but is sometimes diffuse and tubular, or large and oval. A direct surgical repair of the stenosis is not possible in the tubular type. By using selective angiocardiography with the tip of the cardiac catheter in the right ventricle, excellent visualization of the exact anatomy of an infundibular or valvular stenosis is obtained[112].

3) HYPOPLASIA OF THE MAIN PULMONARY ARTERY. In most cases, the main pulmonary artery is diminished in caliber, but in some instances it is normal in size. In severe degrees of pulmonary stenosis, the pulmonary artery is apt to be quite small and fills several seconds after the early opacification of the aorta. In general, the smaller the pulmonary artery becomes, the larger the caliber of the aorta[44]. Post-stenotic dilation of the pulmonary artery occurs much more frequently in a valvular than in an infundibular stenosis; about 20%[47,87] to 30%[102] of cases will have post-stenotic dilatation. Some cases which have an apparent enlargement of the pulmonary artery at fluoroscopy and on plain films will be found at angiocardiography to have a small pulmonary artery and a prominent left upper mediastinum from such other causes as a left superior vena cava[41]. Those having true post-stenotic dilatation at surgery have a thin-walled flabby pulmonary artery containing blood under low pressure[41].

4) DIMINISHED PERIPHERAL PULMONARY VASCULARITY. The decreased pulmonary blood flow can be estimated by the density of the contrast medium in the lung fields, by the decreased caliber of the individual pulmonary artery branches, and by the degree of filling of the left chambers in the later films[21]. Cooley *et al.*[41] considers angiocardiography as the best available method for demonstrating the state of the peripheral pulmonary vascular bed; it, therefore, is useful when the fluoroscopic impression of the pulmonary vascularity is doubtful. The decreased vascularity is good evidence of a pulmonary stenosis when the stenosis cannot be demonstrated directly. In about 20% of cases, however, angiocardiography will fail to show any diminution in the pulmonary vascularity and the patients will nevertheless improve following a Blalock-Taussig anastomosis[21]. Unequal vascularity in the two lungs occurs to some degree in 20% of cases[87] and rarely there is marked unilateral hypoplasia of the vessels. The left main branch is often considerably higher than the right[102].

5) PREMATURE FILLING OF THE LEFT VENTRICLE THROUGH THE HIGH VENTRICULAR SEPTAL DEFECT. Unless the septal defect is quite large, the early filling of the left ventricular area from the right is usually quite faint and is best demonstrated in the left oblique and A.P. views. Rarely, the actual size of the defect is directly seen; in rapid serial films it is usually demonstrated in ventricular systole.

6) ASSOCIATED ANOMALIES OF THE AORTIC ARCH. About 17 to 25% of cases of tetralogy have a right aortic arch, and rarely there is a double arch. The exact course of the arch can usually be determined by ordinary roentgenographic means, but if not, it can be demonstrated by angiocardiography.

7) ASSOCIATED ANOMALIES OF THE BRANCHES OF THE AORTIC ARCH. It is valuable to see the branches of the

aorta so that their suitability for a Blalock-Taussig anastomosis can be determined. An abnormally high origin of the subclavian artery or a prominent aortic arch may make a Pott's anastomosis preferable to the Blalock-Taussig procedure[47]. In intravenous angiocardiograms, the subclavian arteries are clearly outlined in slightly more than half the cases[87]. If necessary, excellent visualization of the aortic branches can be obtained by selective angiocardiography with the catheter tip in the origin of the overriding aorta[112]. Angiocardiography after surgery is useful in determining the patency of an anastomosis; the pulmonary artery branches on the side of anastomosis usually fail to opacify with those of the other side. With marked overriding of the aorta and dense early aortic opacification the side of the anastomosis may fill earlier and more densely than the opposite side[47]. In surgical failures, angiocardiography may show severe kinking of the subclavian artery used in the anastomosis, upward retraction of the pulmonary artery branch, and an absence of the usual asymmetry in opacification of the peripheral pulmonary branches.

About 4% of congenital pulmonic stenoses have aberrant subclavian arteries[7], with the right and left subclavians being involved with about equal frequency. Most of the aberrant vessels are retro-esophageal and, therefore, can easily be demonstrated by barium swallow; a few aberrant vessels, however, run between the trachea and esophagus and these can be demonstrated by angiocardiography[3]. The vessels are best demonstrated in the oblique or A.P. view[163]; the lateral view is unsatisfactory because all of the aortic branches are superimposed. It is highly desirable to perform the injection through a superficial vein of a lower limb; this avoids opacifying the superior vena cava which is apt to overlie the arterial branches. A localized dilatation of the aberrant vessel just at its origin is sometimes demonstrated.

8) NONSPECIFIC CHANGES IN THE RIGHT HEART. Minimal to moderate enlargement of the right auricle and right ventricle is usually demonstrated, and hypertrophy of the right ventricular musculature can be demonstrated in about half of the cases in the left oblique view[102]. The venae cavae are usually dilated and caval refluxes of the contrast medium in atrial systole are common, due to the increased pressure in the right side of the heart[102]. In rapid serial films the amount of residual contrast substance in the right auricle and right ventricle at the end of systole is greater than normal[102]. Anomalies of the venae cavae may be as high as 10%[104], but most of these are of no functional importance.

9) ASSOCIATED PATENT DUCTUS ARTERIOSUS. This usually cannot be demonstrated by angiocardiography. In tetralogy, persistent filling of the pulmonary artery after the right ventricle is empty is suggestive of a patent ductus[204,205]. With rapid serial films, the ductus may be directly visualized[102].

10) ANGIOCARDIOGRAPHIC DIFFERENTIAL DIAGNOSIS OF TETRALOGY[125]. THE EISENMENGER COMPLEX, PERSISTENT TRUNCUS ARTERIOSUS WITH DECREASED PULMONARY FLOW, TRANSPOSITION WITH PULMONIC STENOSIS, SINGLE VENTRICLE WITH PULMONIC STENOSIS, ISOLATED PULMONIC STENOSIS WITH PATENT FORAMEN OVALE. Atypical cases of tetralogy with post-stenotic dilatation of the pulmonary artery and no evidence of decrease in the pulmonary vascularity are readily confused with Eisenmenger's complex. In doubtful cases of this type, the changes in pressure in the pulmonary artery and right ventricle on cardiac catheterization are more reliable than

angiocardiographic findings[41]. Selective angiocardiography may be of definite value in the differential diagnosis, when the presence or absence of a pulmonic stenosis can be definitely established[112].

Pentalogy of Fallot. The angiocardiographic findings are essentially the same as those in the tetralogy of Fallot, but in addition there is premature opacification of the left auricle from the right auricle, best demonstrated in the lateral view. The patent foramen ovale can usually be demonstrated because the shunt is from right to left. The right auricle tends to be somewhat larger and the left chambers are definitely larger than in the tetralogy[70,90]. In the left oblique view, ventricular hypertrophy may be demonstrated on the left side as well as on the right. When rapid serial films are taken, the incidence of patent foramen ovale with right to left shunt, complicating the tetralogy of Fallot, is surprisingly high (approximately 35%)[102], but in many the defect is quite small.

ANGIOCARDIOGRAPHIC DIFFERENTIAL DIAGNOSIS OF PENTALOGY OF FALLOT. The presence of a patent foramen ovale with right to left shunt makes the anomaly much more difficult to differentiate from other anomalies with decreased pulmonary vascularity. It may be difficult to determine whether the early visualization of the aorta is due only to an interauricular shunt, or to an additional overriding of the aorta. It is, therefore, difficult to differentiate from isolated pulmonic stenosis with a patent foramen ovale. In the pentalogy, however, the aorta tends to be considerably more dense than the left ventricle in the early films[87]. In the left oblique and lateral films, the abnormal position of the origin of the aorta may clearly indicate overriding. This anomaly may also be confused with Ebstein's anomaly, tricuspid atresia, single ventricle, or transposition with pulmonary stenosis, all of which may have an atrial septal defect.

Transposition of the Great Vessels. Some authors consider that angiocardiography is the only definite means of proving this anomaly during life[88], while others consider the procedure necessary only in a minority of cases in which the diagnosis cannot be suggested by clinical and routine radiographic methods[128].

1) ABNORMAL ANTERIOR POSITION OF THE ASCENDING AORTA, ARISING FROM THE RIGHT VENTRICLE. In the lateral projection, the ascending aorta is seen immediately behind the sternum arising from the right ventricle. In the left oblique position, the origin of the aorta is seen entirely to the right of the ventricular septum. Early sequential filling of the right auricle, right ventricle and aorta is seen in all projections, with failure of the pulmonary artery to fill, at the same time as the aorta[1]. An abnormally wide sweep of the aortic arch can be demonstrated in both the lateral and left oblique views. There is a tendency for the aorta and its branches to fill in high concentration.

In A.P. views, Holzmann[104] described three common variations in the origin of the aortic arch. The first and common type is the median aortic arch with both the ascending and descending aorta lying close to the mid-line and the arch just to the left of the mid-line; this type gives the classical appearance of transposition on routine films; that is, the shadow of the great vessels is quite narrow compared to the heart size. In the second type, the aortic arch is right-sided. In the third type, the arch is left-sided with marked external rotation. This causes the ascending aorta to lie far to the left of the descending aorta and to form a wide curvature in the left upper medi-

astinal contour. This third type of aortic arch has been wrongly called characteristic of transposition of the great vessels by some authors[87,88]. This peculiar origin of the aorta may at times be seen in other anomalies such as single ventricle and tricuspid atresia[125]. In most cases, there is no significant opacification of the aorta in the later films when the left chambers are opacified, but in unusual cases, reopacification of the aorta may occur[43].

In rare cases, the anterior position of the aorta is not well demonstrated in the left oblique and lateral views, and the position of the aorta simulates a dextro-position; because of the increased pulmonary vascularity, these cases are apt to be wrongly diagnosed as the Eisenmenger complex[43]. A corrected transposition[104] in which the pulmonary veins and venae cavae are transposed into the opposite atria is extremely rare.

2) INCREASED PULMONARY VASCULARITY. The pulmonary artery does not fill synchronously with the aorta as in overriding, but fills later; despite the increased pulmonary vascularity, therefore, very little medium reaches the lungs in the initial films[4]. The main pulmonary artery is often moderately dilated, but this is usually not seen on the A.P. films because of the superimposition of the aorta. In the lateral and left oblique views, the size of the pulmonary artery and its abnormal position behind the aorta can be appreciated. The prominent peripheral pulmonary arteries become opacified with the left chambers. In a small proportion of cases, there is a complicating pulmonic stenosis; this cannot usually be visualized directly, but may be inferred from the small caliber of the main and peripheral pulmonary arteries and their poor opacification in the later films.

3) THE DEMONSTRATION OF THE SHUNTS. In the lateral or left oblique views, premature filling of the left auricle from the right indicates an auricular septal defect. From a correlation of angiocardiographic and postmortem studies, Cooley *et al.*[43] showed that in children patencies of the foramen ovale under 3 mm. are not demonstrable, but over 3 mm. are usually demonstrable in angiocardiograms. These findings are of considerable practial importance, because failure to demonstrate a patent foramen ovale indicates the necessity for the surgical creation of an adequate auricular septal defect. Ventricular septal defects are not demonstrated as well or as frequently as patencies of the foramen ovale, especially when there is a coexisting atrial septal defect. Only rarely can a patent ductus be demonstrated[43].

4) NONSPECIFIC FINDINGS IN THE CARDIAC CHAMBERS. The contrast medium tends to diffuse through the heart and empty from the heart quite rapidly, especially in infants[82]. In adults, angiocardiography often does not give a clear picture of the heart chambers because of the bi-directional shunts; often there is complete clarity only in the early films and only the right chambers are adequately seen[22]. Enlargement of the right chambers is usually present[1,43]. Sometimes transposition is complicated by under-development of one of the ventricles and this can often be demonstrated. For better visualization of the left chambers, selective angiocardiography has been advocated[97] with the tip of the catheter extending through the patent foramen ovale into the left auricle.

5) VISUALIZATION OF THE CORONARY ARTERIES. In routine angiocardiograms, the coronary arteries are visualized in less than 1%[90]. In transposition[43] and also sometimes in the tetralogy of Fallot[90], visualization of the coronary arteries, especially of the left, is not too

unusual, because of the dense early opacification of the aorta.

Taussig-Bing Syndrome. Only a few proven cases of this syndrome have had angiocardiographic studies,[43,125,145,202]. As in the ordinary transposition, the aorta arises from the right ventricle anteriorly immediately behind the sternum. The diagnostic angiocardiographic feature of the syndrome is simultaneous filling of the dilated pulmonary artery and of the aorta in the lateral or left oblique views, differentiating the condition from an ordinary transposition. This unique feature is demonstrated only under favorable circumstances[145]. Some cases of the syndrome on angiocardiograms have been indistinguishable from ordinary transposition[43,202]. In a few cases, the transposition is not well demonstrated in the lateral views and the appearance of the aorta may simulate overriding as seen in the Eisenmenger complex[145]. The condition may also be difficult to differentiate from single ventricle with transposition and increased pulmonary vascularity[145].

Tricuspid Atresia with Hypoplastic Right Ventricle. The angiocardiographic appearance of this anomaly is usually so characteristic that the diagnosis can be made from this study alone; however, the majority of cases can be diagnosed from the clinical, electrocardiographic and routine radiological studies without angiocardiography.

1) DEMONSTRATION OF THE AURICULAR SEPTAL DEFECT. A patent foramen ovale is an invariable part of this anomaly, as life is impossible without it. In the early lateral or left oblique films all the medium in the right auricle extends through the patent foramen ovale into the left auricle. In rapid serial films the size of the patent foramen ovale may be visualized directly; this is important because cases with a small patent foramen ovale and slow filling of the left auricle will require an artificial auricular septal defect as well as a Blalock-Taussig anastomosis. In the later films, there is never any reopacification of the right auricle[82] because the flow through the patent foramen ovale is entirely from right to left; if definite reopacification of the right auricle is seen, this anomaly can be excluded.

2) DEMONSTRATION OF THE HYPOPLASTIC RIGHT VENTRICLE. The characteristic angiocardiographic signs of this anomaly are signs of hypoplasia of the right ventricle, a fundamental part of the anomaly; the stenosis or atresia of the tricuspid valves is not directly demonstrated, but inferred. With sequential filling of the right auricle, left auricle, and left ventricle, a large triangular unopacified area[42,143] (representing the hypoplastic right ventricle) remains in the lower border of the heart between the right auricle and left ventricle, in the A.P. and left oblique views. The latter view may be preferable because the triangular area is often obscured by the thoracic spine in the A.P. projection. In the lateral views, the rudimentary right ventricle is an abnormal unopacified space in the angle between the lower sternum and anterior right dome of the diaphragm; normally this area opacifies completely with filling of the right ventricle[42].

In atypical cases, there may be only slight underdevelopment of the right ventricle; in others, the right ventricle may be almost completely absent and the angiocardiographic picture may then resemble that of a single ventricle. In rare cases the rudimentary right ventricle may occur without any tricuspid stenosis or atresia. Immediate but poor opacification of the rudimentary right ventricle from the right auricle indicates a tricuspid stenosis rather than an atresia.

3) ENLARGEMENT OF THE RIGHT AU-

RICLE, LEFT AURICLE AND LEFT VENTRICLE. Although there is usually no generalized cardiac enlargement, the right auricle, left auricle and left ventricle are usually dilated. The "textbook" heart contour of tricuspid atresia with an abnormally straight and shallow right heart border is not often present, because of the marked enlargement of the right auricle[143].

4) HYPOPLASIA OF THE PULMONARY ARTERY WITH DIMINISHED PERIPHERAL PULMONARY VASCULARITY. There is usually some form of pulmonary stenosis, but the exact site is not well demonstrated by angiocardiography[143]. The main pulmonary artery is usually hypoplastic, sometimes atretic, and uncommonly it is normal in size[42]. The peripheral pulmonary vascularity is diminished except when there is transposition of the great vessels. There are four possible sources of the pulmonary blood supply and these sources can often be demonstrated: ventricular septal defect, transposition of the great vessels, patent ductus arteriosus, or tricuspid stenosis with some degree of filling of the right ventricle.

5) VENTRICULAR SEPTAL DEFECT. Opacification of the pulmonary artery immediately following the filling of the left ventricle indicates a ventricular septal defect. In about one-third of the cases of tricuspid atresia, there is opacification of the rudimentary chamber in the later films indicating a ventricular septal defect. In the other two-thirds of the cases, the rudimentary chamber remains unopacified throughout the examination[42].

6) ASSOCIATED TRANSPOSITION OF THE GREAT VESSELS. In the series of Cooley *et al.*[42], transposition occurred in about one-third of the cases of tricuspid atresia, with increased peripheral pulmonary vascularity.

7) ASSOCIATED PATENT DUCTUS ARTERIOSUS. Sometimes the patent ductus arteriosus is directly visualized, and according to some authors[126] this occurs more commonly than in other anomalies associated with a patent ductus. Reopacification of the left auricle is rarely seen in tricuspid atresia, but when it occurs it is good evidence of an associated patent ductus[47].

Rarely, a case with the angiocardiographic appearance of tetralogy of Fallot will have tricuspid atresia at postmortem examination. One such case at The Johns Hopkins Hospital had right axis deviation and at necropsy a rudimentary right ventricle was found, the right ventricular wall being exceptionally thick.

Coarctation of the Aorta. 1. DEMONSTRATION OF THE STENOTIC SEGMENT. Most authors prefer the true lateral or left oblique view to demonstrate this anomaly, but many of the features can be demonstrated on the A.P. view. Although the anatomical details are often seen in angiocardiograms, especially in children, thoracic aortography provides better visualization of the details in adults[184]. Satisfactory visualization is achieved in about 90% of contrast studies[74]. The location, length, and degree of stenosis can usually be determined. The classification of coarctations into "infantile" and "adult" types is not helpful from a surgical viewpoint[184]. In about 97% of cases, the stenosis is at the "usual" site, that is, between the origin of the left subclavian artery and just distal to the insertion of the ligamentum arteriosum[184]. In the majority, the stenosis is well localized but about 8% have a diffuse stenosis which is not amenable to the usual surgical end-to-end anastomosis. About 3% of coarctations[183] have stenoses at atypical sites, either in the aortic arch proximal to the left subclavian artery or in the lower thoracic or abdominal aorta[8,78,184]. Many of these atypical cases are not amenable to surgical re-

section[8]. In the abnormally low coarctations, there is usually either no notching of the ribs or notching of only the lower ribs[8]. When surgical resection is being considered, an important point to observe is the distance between the origin of the left subclavian artery and the site of coarctation[8]. Sub-clinical cases of coarctation with only slight narrowing have been demonstrated by aortography[78]. In 13%[87] to 31%[184] the concentration of the contrast medium in the aorta on angiocardiography is rather poor; in these cases errors in estimating the true length of the stenotic segment are apt to be made. Furthermore, in the lateral films of these cases, the shadow of the left upper lobe bronchus crossing the faintly opacified aorta can easily be mistaken for the site of coarctation[8]. In rapid serial angiocardiography in children[209], it has been demonstrated that the caliber of the stenosis becomes larger in ventricular systole than in diastole. In the lateral films, there is often a forward "dislocation"[113] or antero-medial "buckling"[74] of the aorta at the stenotic site produced by the traction of the ligamentum arteriosum. Rarely, this buckling effect of the aorta may occur without any coarctation. In infants, the stenosis tends to be more diffuse and to be located closer to the left subclavian origin than in adults[8]. In the A.P. views, a localized indentation of the aorta or "figure 3" deformity is often seen in the region of the aortic knob; from correlation of plain Roentgen-ray films, contrast studies and surgical findings, it has been shown that the indentation in most cases is due to the actual stenotic site; however, in a few cases it has been due to angulation between the left subclavian artery and the distal arch[74].

2. CHANGES IN THE AORTA PROXIMAL TO THE COARCTATION. In about half the cases, there is slight to moderate dilatation of the ascending aorta, but this structure is often of normal caliber and uncommonly it is hypoplastic. In cases with extreme dilatation of the ascending aorta, aortic insufficiency is apt to be present clinically[74]. A reduction in the caliber of the transverse arch between the left carotid and subclavian arteries is a fairly constant feature and in most cases its diameter is about half that of the ascending aorta[74]. Aortography in infants is often valuable in revealing segmental or diffuse hypoplasia of the arch[125].

3. CHANGES IN THE AORTA DISTAL TO THE COARCTATION. Post-stenotic dilatation of the aorta is demonstrated in about 75% of cases[87]; sometimes the descending aorta is diffusely hypoplastic. In many cases, especially in infants and children, the descending aorta is normal in caliber. In the lateral view, the descending aorta often runs either vertically downward, or downward and forward, instead of the normal downward and backward course[177]. In cases with little or no opacification of the distal aorta in spite of dense opacification up to the stenotic area, there is either complete or almost complete stenosis; delayed films in such cases may show faint filling of the distal aorta from the collateral circulation. The complete coarctations are seen more commonly in infants than adults. Aortography may prove valuable in cases with marked post-stenotic dilatation in demonstrating or ruling out the presence of an associated dissecting aneurysm. If dense opacification of the aorta is obtained, it may even be possible to detect secondary arteriosclerotic changes by observing roughening of the contour of the dye column.

4. THE COLLATERAL CIRCULATION. The dilated scapular, internal mammary and intercostal arteries forming the collateral circulation can usually be demonstrated by contrast methods. The

intercostals are often best demonstrated in oblique views[70] and the internal mammaries in the lateral views[156]. Dilated tortuous intercostal arteries forming "loops and whorls" were first demonstrated as a specific indirect sign of coarctation in aortograms by Pereiras and Castellanos[31]; they pointed out that notching of the ribs is usually not seen in infancy because the intercostal vessels are somewhat separated from the overlying ribs and that this separation disappears in later life. Aneurysms of the intercostal arteries are found in about 10% of cases at surgery[184]; only occasionally can they be demonstrated in the contrast studies as a localized outpouching just outside the aorta. In mild coarctation, there may be no development of collateral circulation[74]. In younger children with marked disability and decompensation from coarctation, there may also be little or no evidence of development of collaterals[158]. In one case at aortography, an anomalous branch of the left coronary artery participating in the collateral circulation was demonstrated[53].

5. ASSOCIATED ABNORMALITIES OF THE AORTIC BRANCHES. A localized dilatation of the origin of the left subclavian artery which forms a prominence in the left upper mediastinal contour is often demonstrated[70]. Occasionally, an aberrant subclavian artery is associated with coarctation. When the left subclavian arises distal to the stenosis there is notching of the right ribs only. When the right subclavian or innominate arise distal to the stenosis, there is notching of the left ribs only. These aberrant vessels are often retro-esophageal and have been demonstrated by aortography[17]. In atypical coarctation, the stenosis is rarely entirely limited to the origin of the left subclavian artery[146]. More frequently, cases have been encountered with only slight, but diffuse narrowing of the aorta and stenosis of the left subclavian origin, causing poor filling of the left subclavian artery with contrast medium and an absent radial pulse[95].

6. ASSOCIATED CHANGES IN THE HEART. In patients over the age of 2 years, with coarctation the heart is normal in size and contour in about 60%[74]; slight cardiac enlargement occurs in about 20% and definite enlargement of the left ventricle in 20%. A significant number of younger children[158] have definite cardiac enlargement and decompensation secondary to the coarctation; aortograms in these cases are apt to show rather marked hypoplasia of the aortic arch.

7. ASSOCIATED PATENT DUCTUS ARTERIOSUS. In adults about 6% of cases of coarctation will have a patent ductus arteriosus at surgery[184]; a greater number of these will be diagnosed before surgery by aortography than by angiocardiography.

8. POSTOPERATIVE FEATURES. In the usual postoperative aortogram, a minor constriction remains at the site of the end-to-end anastomosis. The average waist-like constriction postoperatively is about 60 to 70% of the normal lumen[177]. Functioning end-to-side anastomoses between the left subclavian and poststenotic segment can also be demonstrated[113]. At 7 months postoperatively, the internal mammary arteries may show only slight regression in some cases and complete disappearance in others[156]. Surgical "failures" after resection are apt to show a narrow anastomotic segment, marked hypoplasia of the descending aorta, or no regression in the size of the internal mammary collaterals[156]. In a few cases[177,184] thin-walled postoperative aneurysms will develop just beyond the suture site.

Patent Ductus Arteriosus. In spite of the long and varied list of signs which have been described in angiocardiograms and aortograms in patent ductus

arteriosus, contrast studies in this anomaly are often nonspecific and uninformative[59,144]. The roentgenological signs are usually present in adults with the anomaly, where the diagnosis can usually be made on the basis of the continuous or "machinery" murmur. Contrast studies are necessary in this anomaly only in a few atypical cases without a continuous murmur; these diagnostic difficulties occur usually in infants and children and unfortunately in this group most of the roentgenological signs are unreliable[59,87,125,144]. The best projections for the demonstration of this anomaly are the left oblique and left lateral.

1. RETROGRADE FILLING OF THE PULMONARY ARTERY FROM THE AORTA IN THORACIC AORTOGRAPHY. In the diagnostic problems of infancy and childhood, this sign is often the only radiological indication of a patent ductus with a left to right shunt. The retrograde flow of the contrast medium from the aortic arch into the pulmonary artery tends to spread to the left descending branch of the pulmonary artery[114] and often the other branches are unopacified. Even in the use of this method, several cases of patent ductus arteriosus have been missed at The Johns Hopkins Hospital, especially when a good concentration of the contrast medium has not reached the aortic arch. In thoracic aortograms in adults with the injection made through a catheter, filling of the pulmonary artery from the aorta can be demonstrated in all cases[112].

2. THE INFUNDIBULUM OF THE DUCTUS. This sign was first described by Steinberg, Grishman and Sussman in 1943[193] as a distinctive localized dilatation of the descending aorta just beyond the isthmus. It probably consists of a traction aneurysm at the site of attachment of the ductus, and projects toward the main and left pulmonary arteries. They considered the infundibulum to be a pathognomonic sign of a patent ductus and demonstrated it in 26 out of 27 angiocardiograms in adults with the anomaly. Occasionally, the infundibulum appeared as a localized fusiform dilatation of the proximal descending aorta. In 27 thoracic aortograms in adults, Jönsson[119,120] demonstrated the infundibulum in all but 2 cases. Considerable variation in the size of the structure was noted, sometimes being large and funnel-shaped, sometimes merely a shallow bulge. While it is usually in the upper descending aorta, it is sometimes in the center of the arch. In 3 out of 4 normal aortograms, a small infundibulum was seen, due to traction of the ligamentum arteriosum, but the structure did not project more than one millimeter. In rapid serial angiocardiography in children, a momentary lingering of the contrast medium in the infundibulum after the aorta has cleared has been noted. The infundibulum in children, however, is usually either inconspicuous or absent[194]. Some authors[87,144] do not consider the infundibulum to be pathognomonic because it has been observed in several cases without patent ductus; many cases in adults have been encountered in which the infundibulum was absent even at surgery[144].

3. THE JET SIGN. This sign was first described by Goetz[85] as a filling defect in the opaque column of the main pulmonary artery produced by the stream of unopacified blood emerging from the aorta by way of the ductus; the defect is visible only in early films before the aorta is opacified and the appearance may be quite transient. The defect may be seen in the A.P. views, but is best seen in the left oblique projection. In rapid serial angiocardiography[209], this sign has been sometimes seen only transiently on a single film, usually during ventricular diastole; with this technique, the "jet" sign is probably

the most specific angiocardiographic sign of patent ductus in infants and children. Dotter and Steinberg[60] also described a similar dilution effect in the left pulmonary artery.

4. RE-OPACIFICATION OR CONTINUED OPACIFICATION OF THE PULMONARY ARTERY. Many authors feel that this feature has been greatly over-emphasized[87,127,193,204,205] because it may occur with any type of left-to-right shunt. In most cases there is only a continued or prolonged opacification of the pulmonary artery rather than a re-opacification[127]. A false appearance of re-opacification may easily be produced by slight variations in radiographic technique in serial films. The sign of re-opacification may be more significant if, in the left oblique view, the right ventricular area is entirely clear of contrast medium[144].

5. DILATATION OF THE PULMONARY ARTERY AND INCREASED PERIPHERAL PULMONARY VASCULARITY. The main and major branches of the pulmonary artery are dilated in about 80% of adults and in 30% the dilatation is marked[193]. Progressive aneurysmal dilatation of the pulmonary artery sometimes occurs[144]. Aneurysmal dilatation confined to a main pulmonary artery branch has been observed[141]. True aneurysms of the patent ductus proper are rare, and apparently none has yet been demonstrated by contrast studies. In angiocardiocinematography[108], unusually strong and rhythmic lateral motion of the entire pulmonary artery has been demonstrated.

6. TRACTION ON THE PULMONARY ARTERY. Steinberg, Grishman, and Sussman[193] described elevation of the main and left pulmonary artery suggesting that they are being drawn toward the aorta by the ductus. Kreutzer[132] described a localized dilatation of the pulmonary artery at the point where the ductus enters.

7. ENLARGEMENT OF THE LEFT CHAMBERS. This occurs in about two-thirds of the cases[193]; although the finding is nonspecific, it may be of value in an acyanotic patient with a suspected left-to-right shunt[144].

8. DIRECT VISUALIZATION OF THE DUCTUS. This is observed only occasionally even with a rapid serial technique. The opacification of the ductus apparently is quite transient in ventricular systole and is seen in the lateral or left oblique only when the left auricle is not in full diastole[209]. In thoracic aortograms, it is occasionally seen in children, and it is often so clearly seen in adults that its length and caliber can be estimated[113].

9. PATENT DUCTUS WITH REVERSED FLOW. Not all cases with a reversed flow demonstrated by angiocardiography have cyanosis of the lower limbs and lower trunk. The classical angiocardiographic finding[82,144] is premature opacification of the descending aorta simultaneously with the pulmonary artery, without opacification of the ascending aorta. In these cases, the patent ductus is apt to be fairly large and is often directly visualized. In the later films of the series showing opacification of the left heart chambers, there is good opacification of the ascending aorta, but beyond the insertion of the ductus the contrast medium is suddenly diluted. The pulmonary vascularity is usually markedly increased, the pulmonary artery markedly dilated, and the right ventricle as well as the left is often enlarged. Sometimes the reversal of the flow is due only to marked pulmonary hypertension; associated anomalies which cause pulmonary hypertension, however, are quite common. These include congenital mitral stenosis[68], aortic stenosis, hypoplasia, coarctation or complete interruption of the aortic arch proximal to the ductus attachment.

10. POSTOPERATIVE CHANGES. Angiocardiography in one case postoperatively showed a persistence of the infundibulum following ligation, but the re-opacification of the pulmonary artery from the aorta which had been demonstrated pre-operatively no longer occurred[123].

11. ANGIOCARDIOGRAPHIC DIFFERENTIAL DIAGNOSIS. This anomaly may be confused with other conditions which cause dilatation of the pulmonary artery[34,86,150]; that is, congenital aneurysm of the pulmonary artery[149], idiopathic dilatation of the pulmonary artery[86], isolated pulmonic stenosis, auricular or ventricular septal defect, primary pulmonary hypertension, cor pulmonale, Eisenmenger's syndrome, congenital mitral stenosis and rheumatic heart disease.

Atrial Septal Defect. 1. DEMONSTRATION OF THE SHUNT FROM THE RIGHT TO THE LEFT ATRIUM. The best projections to demonstrate this anomaly are the true lateral or left oblique, the positions in which the two atria are well separated. It has been well established that angiocardiography is a valuable procedure for the demonstration of right-to-left auricular shunts. These are associated with cyanosis and hypertension in the right chambers in such anomalies as tricuspid atresia, Ebstein's anomaly, transposition, pulmonic stenosis, tetralogy of Fallot[87]. The value of angiocardiography in uncomplicated auricular septal defects with left-to-right shunts is controversial. It should be used only in problem cases which have not been clarified by clinical methods and cardiac catheterization. The only specific angiocardiographic sign in these cases is the demonstration of premature opacification of the left auricle from the right; in order for this to happen, the shunt must be bi-directional, or the flow through the shunt must be temporarily reversed by the force of injection. Most of the early writers on angiocardiography were unable to demonstrate any premature opacification of the left auricle and concluded that angiocardiography was of no value[46,47,59]. Sussman, Grishman and Steinberg[192] obtained premature filling of the left auricle in only one adult out of 10 cases. Several authors have reversed the shunt through the defect occasionally in infants and small children by rapid injection[47,59,82,87,125]. Most authors state, however, that it is not possible to reverse the flow in adults. In children, the chances of showing the defect are greater in cases with large defects[82].

If reversal of the flow through the shunt has been obtained, there is a premature opacification of the left auricle, left ventricle, and aorta (levogram), and the left heart becomes opacified again at the normal time, (bi-directional levogram)[104]. In A.P. films, after a reversal of the shunt has been obtained, the left atrial area is poorly seen, and the premature opacification of the left ventricle and aorta may produce a false appearance of an overriding aorta.

By rapid bi-plane serial angiocardiography at ten films per second, Lind and Wegelius[137] were able to demonstrate premature opacification of the left auricle in a much higher percentage of cases than had been obtained previously, and thereby established the value of angiocardiography in this anomaly. They claimed that many shunts are actually bi-directional and that the extremely short period of right-to-left flow will be demonstrated only in rapid serial films. In bi-directional shunts, the left auricular opacity is most marked in atrial systole, as indicated in the simultaneous electrocardiogram; in "pure" left-to-right shunts, the left auricular opacification is seen only in atrial diastole. These authors

also claimed that in infants and young children an auricular septal defect is better demonstrated when the injection is made in the lower limb, rather than the upper limb, thereby using the path of the fetal circulation[134,137]. In angiocardiograms of infants and fetuses, they demonstrated that the patent foramen ovale is usually still open 12 hours after birth but is always normally closed after the sixth day.

Premature left atrial opacification of only slight degree indicates that the shunt is quite small and less significant[125,137]. In a patent foramen ovale of small size the flow of media into the left auricle is apt to be intermittent; in large defects the flow tends to be more continuous[125].

2. DEMONSTRATION OF THE ACTUAL SIZE OF THE DEFECT. In auricular septal defects with shunt from right to left associated with other anomalies, the actual size of the defect can be seen in about one-sixth of the cases[87]. In uncomplicated auricular septal defects, the chances of demonstrating the size of the shunt are much less. It is the size of the defect relative to the heart size which is important clinically, rather than the defect's absolute size[137]. Lind and Wegelius[137] demonstrated that the size of the defect is not constant throughout the heart cycle, being larger in atrial diastole than in systole.

3. PERSISTENT OPACIFICATION OR RE-OPACIFICATION OF THE RIGHT CHAMBERS AND PULMONARY ARTERY. On theoretical grounds, an auricular septal defect with a left-to-right shunt should produce re-opacification of the right auricle, right ventricle, and pulmonary artery in the later films following opacification of the left chambers[104]. Unequivocal re-opacification, however, is demonstrated only rarely[104,125,137,192]. Prolonged opacification of the right chambers and pulmonary artery without re-opacification is the rule[125].

4. NONSPECIFIC ENLARGEMENT OF THE RIGHT CHAMBERS AND DILATATION OF THE MAIN AND PERIPHERAL PULMONARY ARTERIES. In clinically significant uncomplicated atrial septal defects, enlargement of the right auricle, right auricular appendage and right ventricle can usually be demonstrated. When enlarged, the right ventricle may occupy the left border of the heart on A.P. films[137]. In comparison, the left chambers usually appear small and the aorta often appears hypoplastic compared with the dilated pulmonary artery. In rapid serial films, an increased amplitude of the pulsations of the pulmonary artery is demonstrated[137]. In many cases, the opacification of the left chambers and aorta may be quite poor throughout the examination.

5. NONSPECIFIC CAVAL REFLUXES. From a study of rapid serial angiocardiograms and simultaneous electrocardiograms, Hedman, Lind, and Wegelius[99] claim that reflux of the contrast medium into the venae cavae in auricular diastole may occur normally due to the increased pressure from the force of injection, but that refluxes in atrial systole are indicative of abnormally high pressure in the right auricle. In a few cases, however, reflux has been demonstrated in auricular systole without increased pressure being evident on cardiac catheterization.

Ventricular Septal Defect. 1. DIRECT DEMONSTRATION OF THE SHUNT FROM THE RIGHT VENTRICLE TO THE LEFT VENTRICLE. When a ventricular septal defect is associated with anomalies which cause hypertension in the right chambers, (that is, overriding of the aorta, transposition or pulmonic stenosis), a premature opacification of the left ventricle from the right can usually be demonstrated and occasionally the actual size of the defect may be seen. These findings are best demonstrated in A.P. and left oblique views. In un-

complicated ventricular septal defects with a left-to-right shunt, a reversal of the flow with early opacification of the left ventricle can rarely be obtained[59, 192] unless the defect is quite large. In the common type of clinically insignificant small ventricular septal defect (Maladie de Roger), the angiocardiograms are usually perfectly normal. In the less common high ventricular septal defect in the membranous portion of the ventricular septum immediately beneath the aortic valve, seen usually in children, there is often simultaneous opacification of the pulmonary artery and aorta from the right ventricle, with faint opacification of the left ventricle[82]. In this type with pulmonary hypertension, it may be difficult or impossible to differentiate from an Eisenmenger's complex with minimal overriding of the aorta[82].

2. NONSPECIFIC ENLARGEMENT OF THE RIGHT CHAMBERS AND DILATATION OF THE MAIN AND PERIPHERAL PULMONARY ARTERIES. Significant chamber enlargement is seen only in the high ventricular septal defects.

3. PROLONGED OPACIFICATION OR RE-OPACIFICATION OF THE RIGHT VENTRICLE AND PULMONARY ARTERY. As in auricular septal defect, re-opacification of the right ventricle and pulmonary artery is rarely definite; prolonged opacification of the right chambers and pulmonary arteries is seen only with clinically significant defects and the finding is nonspecific[125].

Isolated Pulmonic Stenosis (Pulmonic Stenosis with Intact Ventricular Septum). 1. DEMONSTRATION OF THE STENOTIC SITE. Angiocardiography is not an essential part of the diagnostic investigation of most cases of this anomaly, when the clinical and catheterization data are adequate. The angiocardiogram, however, may be of value in doubtful cases, especially where the catheter cannot be inserted into the pulmonary artery; it is also of value in differentiating the more common pulmonic valvular stenosis from the less common isolated stenosis of the infundibulum. The pulmonary valve cusps or site of stenosis can be demonstrated in about 75% of angiocardiograms[87], a much better percentage than when overriding is present. The site may be demonstrated in either A.P. or lateral views, but the right oblique view is the ideal projection[82]. In minimal degrees of pulmonic stenosis, it has been said that with either angiocardiography or catheterization one may confirm but never exclude the diagnosis[59]. It is usually easier to rule out an infundibular stenosis and infer a valvular stenosis than to directly demonstrate the stenotic valve[21]. By intravenous angiocardiography, even with rapid serial films, it has not been possible to demonstrate the size of the orifice of the stenotic valve[47,69,87,180]. By using selective angiocardiography with the tip of the catheter in the outflow tract of the right ventricle[113], however, excellent visualization of the stenotic site has been obtained and the exact size of the orifice can be seen in systole. The rigidity of the valves can also be observed in rapid serial films in this method; the valves do not fall back as they should in diastole, but tend to form a "dome-shaped protuberance." Above the stenosis, whirlpools of contrast medium and uneven opacification are often seen in the pulmonary artery. In some cases on selective angiocardiography, hypoplasia of the main pulmonary artery may be found without evidence of valvular or infundibular stenosis[113].

2. POST-STENOTIC DILATATION OF THE PULMONARY ARTERY. In valvular stenoses, this occurs in the majority of cases and is readily demonstrated by angiocardiography. Post-stenotic dilatation is

not as common with the infundibular type.

3. DECREASED PERIPHERAL PULMONARY VASCULARITY. When the pulmonary artery's peripheral branches become opacified, they are usually smaller in caliber than normal and are often poorly opacified[44], in contrast to the dilatation of the main pulmonary artery. In a few cases, the caliber of the branches is normal.

4. NONSPECIFIC ENLARGEMENT OF THE RIGHT CHAMBERS IS COMMON. In rapid serial angiocardiograms, the amount of residual contrast medium in the right chambers at the end of systole is increased above the normal[208]. Because of the increased pressure, caval refluxes in auricular systole are common.

5. ASSOCIATED PATENT FORAMEN OVALE. When present, this can usually be demonstrated as a premature opacification of the left auricle from the right, because the shunt is usually a right-to-left one. Cyanosis is common in this group. In one series patency of the foramen ovale was present in 60% of angiocardiograms[87]. As a result of the early filling of the left auricle, there is also early filling of the left ventricle and aorta.

6. GENERALIZED SLOWING OF THE CIRCULATION. It is well to remember that in the absence of a shunt, there is no specific "hold-up" of the contrast medium proximal to the stenotic pulmonary valve, but rather a generalized slowing of the entire circulation. Because of the marked differences in chamber size, the right chambers will remain opacified for prolonged periods and the left chambers will be very poorly opacified throughout the examination. In mild degrees of stenosis the circulation times may be normal.

7. DIFFERENTIAL DIAGNOSIS WITH A PATENT FORAMEN OVALE. Isolated pulmonic stenosis may closely mimic the tetralogy of Fallot on A.P. films; poststenotic dilatation of the pulmonary artery may be present in both conditions although it is more common in the former. The early filling of the left ventricle in the tetralogy of Fallot tends to be more incomplete and "spotty"[104] than when it is opacified from the left auricle. A normal site of origin of the ascending aorta and early filling of the left auricle in the lateral view will help to exclude a tetralogy[44]. An isolated pulmonic stenosis may be indistinguishable from a congenital aneurysm or dilatation of the pulmonary artery angiocardiographically[59].

The Eisenmenger Complex. 1. OVERRIDING OF THE AORTA WITH SIMULTANEOUS FILLING OF THE PULMONARY ARTERY AND AORTA FROM THE RIGHT VENTRICLE[47, 82,87,104,192]. This is demonstrated in the A.P. view, and the aorta is usually of smaller caliber than the pulmonary artery. In the left oblique and lateral views, the abnormal anterior origin of the aorta partially from the right ventricle is usually well demonstrated. In a few cases, however, there will be no early opacification of the aorta with the pulmonary artery[82], especially when the degree of overriding is slight; it is then usually impossible to differentiate the Eisenmenger complex from a high ventricular septal defect. Because of this, some authors prefer to place both anomalies into an "Eisenmenger's group"[82,87].

2. MARKED DILATATION OF THE MAIN PULMONARY ARTERY. The dilatation is often aneurysmal in degree. The opacification of the pulmonary artery on early films is always denser than that of the aorta, thereby differentiating the anomaly from transposition[104].

3. DILATATION OF THE PERIPHERAL PULMONARY ARTERY BRANCHES WITH DENSE OPACIFICATION. This is well demonstrated in the majority of cases; however, in a certain number of older patients[87] the peripheral pulmonary ar-

teries tend to become narrowed, tortuous and irregular due to secondary pulmonary arteriosclerosis. In some of these cases, the picture will be indistinguishable from the tetralogy of Fallot[87].

4. EARLY FAINT OPACIFICATION OF THE LEFT VENTRICLE FROM THE HIGH VENTRICULAR SEPTAL DEFECT.

5. NONSPECIFIC CHANGES IN THE HEART CHAMBERS. There is usually demonstrable enlargement of the right auricle and right ventricle. In the later films, there may be re-opacification of the right ventricle from the contrast medium extending through the ventricular septal defect[82]. Also, in the later films, the left chambers are usually better visualized than in the tetralogy of Fallot[47].

Ebstein's Anomaly. 1. DEMONSTRATION OF THE DISPLACEMENT OF THE TRICUSPID MEMBRANE TO THE LEFT. This is the only specific angiocardiographic sign of this anomaly, best seen in A.P. or right oblique views; often the only indication of this will be a slight notching of the medium along the inferior border of the heart[68]. In some cases, the site of the displaced membrane will not be seen, and the diagnosis will be rendered difficult[87].

2. DILATATION OF THE RIGHT ATRIUM, AND THE RIGHT VENTRICLE PROXIMAL TO THE TRICUSPID MEMBRANE. The dilated right auricle and proximal portion of the right ventricle form a single dilated cardiac cavity.

3. ABNORMAL THINNING OF THE WALL OF THE PROXIMAL RIGHT VENTRICLE. This is a fundamental part of the anomaly[68], which may at times be detected in the left oblique view. In rapid serial films, irregularity in the pulsations of the right auricle and thin-walled right ventricle may be detected; sometimes the pulsations are quite feeble with very little change in systole and diastole[87].

4. GENERALIZED SLOWING OF THE CIRCULATION. There is often marked generalized slowing of the circulation, and as a result, there is prolonged opacification of the right chambers. However, in the absence of shunts, there is no specific "hang-up" of the contrast medium in the dilated right auricle and thin-walled proximal right ventricle, at the site of the malformed tricuspid valve. Because of the slow circulation and small size of the left chambers, the opacification of the left side of the heart is often poor throughout the examination.

5. HYPOPLASIA OF THE MAIN PULMONARY ARTERY AND DECREASED PERIPHERAL PULMONARY VASCULARITY. The main pulmonary artery is usually small, but is occasionally normal in size. The peripheral pulmonary vessels are decreased in caliber and are opacified poorly.

6. PATENT FORAMEN OVALE. In about two-thirds of the cases[68], there is a patent foramen ovale with a right-to-left shunt, so that premature filling of the left auricle from the right can usually be demonstrated.

7. DIFFERENTIAL DIAGNOSIS. Both cardiac catheterization and angiocardiography[125] may be somewhat dangerous in this anomaly; both procedures, however, may be important in certain cases where the differential diagnosis lies between Ebstein's anomaly and isolated pulmonic stenosis. It is important to diagnose the Ebstein's anomaly correctly to avoid performing surgical procedures which are of no benefit. Both isolated pulmonic stenosis and the Ebstein's anomaly may have patent foramen ovale and cyanosis; both may have apparent enlargement of the right chambers and decrease in the peripheral pulmonary vascularity; on angiocardiography, there will be prolonged opacification of the enlarged right chambers in both con-

ditions; the differential diagnosis will depend on the location of the atrioventricular notch along the inferior border of the heart in the A.P. or right oblique view; if this cannot be clearly identified, differentiation may be impossible. Rarely a pulmonic stenosis and Ebstein's anomaly may occur together[87].

Occasionally, Ebstein's anomaly may be confused with tricuspid atresia[82] because both conditions have decreased vascularity and the course of the circulation is often quite similar in the two conditions, that is, from the right auricle through an auricular septal defect into the left auricle and left ventricle. In Ebstein's anomaly, however, some contrast medium will be seen extending from the right auricle into the distal right ventricle; furthermore, the rudimentary right ventricle can usually be conclusively demonstrated in tricuspid atresia.

Persistent Truncus Arteriosus. A. TRUNCUS ARTERIOSUS WITH DECREASED PULMONARY FLOW. A persistent truncus arteriosus with decreased pulmonary flow may be either a "pseudo-truncus" with an atretic pulmonary artery or a type of "true" truncus with no vistigial trace of a pulmonary artery. These two types cannot be differentiated by contrast methods.

1. Complete absence of a main pulmonary artery shadow. In angiocardiography, the complete failure to opacify a main pulmonary artery shadow is the distinctive feature differentiating from other anomalies[41]. The infundibular region of the right ventricle can be seen ending in a blind peak[44] in A.P. or right oblique views.

2. Early opacification of the aorta. The aorta fills densely and prematurely from the right ventricle. The origin of the aorta usually is in a position of severe overriding as seen in the lateral and left oblique views. It tends to be larger in caliber and more elongated than in the tetralogy of Fallot[82,87]. In a few cases, the ascending aorta may arise far to the left as is more commonly seen in some types of transposition and single ventricle[87].

3. Ventricular septal defect. At the time of filling of the aorta from the right ventricle, some opacification is usually seen in the left ventricular area from the contrast medium extending across the high ventricular septal defect.

4. Marked decrease in peripheral pulmonary vascularity. Peripheral pulmonary arterial branches, if visible at all, are of narrow caliber, and opacify poorly and late. Following opacification of the aorta, the pulmonary arteries may fill from a patent ductus arteriosus[82].

5. Opacification of the bronchial collaterals. After the aorta has become opacified a fine lace-like pattern of contrast medium or a fine stippled pattern may be seen extending out into the lung fields, representing opacification of the dilated bronchial collaterals; rarely large bronchial trunks are opacified[87].

6. Enlargement of the right chambers. Although the heart is usually not generally enlarged, there is often some degree of enlargement of the right auricle and right ventricle[41].

7. Occasionally, an associated tricuspid atresia or a single ventricle is demonstrated[87].

8. Differential diagnosis. Uncommonly in the tetralogy of Fallot, a severely stenotic pulmonary artery may completely fail to opacify at angiocardiography; therefore, a severe pulmonary stenosis cannot always be differentiated from a pulmonary atresia[41]. This is unfortunate, because cases which show no main pulmonary artery cannot be excluded from surgery; occasionally, an unopacified pulmonary artery will be

large enough to perform a Blalock-Taussig anastomosis. Sometimes there is difficulty in distinguishing a truncus with decreased pulmonary flow from a transposition of the great vessels with pulmonary stenosis.

B. TRUNCUS ARTERIOSUS WITH INCREASED PULMONARY FLOW. In this type of "true" truncus arteriosus, the single trunk arises from both ventricles and gives off pulmonary artery branches directly. The clinical and chest roentgenographic findings are usually so characteristic in this anomaly that angiocardiography is scarcely necessary. The single trunk opacifies prematurely from the right ventricle with simultaneous filling of its large pulmonary artery branches; all of the peripheral pulmonary artery branches are markedly dilated. The truncus and aortic arch are much larger than normal. There is often some degree of ventricular enlargement. In cases where the truncus branches at a low level into the aorta and main pulmonary artery, it may be difficult to differentiate from a large aortico-pulmonary septal defect; in this latter condition, however, the aorta usually does not fill as densely or as early as in truncus arteriosus.

Anomalous Pulmonary Venous Return. A. TOTAL ANOMALY OF THE PULMONARY VENOUS RETURN. In this group of anomalies, all of the pulmonary veins have an aberrant insertion, none entering the left auricle; inevitably there is an auricular septal defect which is usually the only pathway for the blood to enter the left side of the heart from the right.

1. Total anomaly of the pulmonary venous return to the left innominate vein. Most angiocardiograms of anomalous venous return in the literature are of this type[91,109,133,186]. The marked bulging of the upper mediastinum on either side, producing the so-called "figure of 8" or "snowman" contour seen on the plain chest films is so characteristic that angiocardiography is not essential to the diagnosis but demonstrates the anatomical details well. Immediately following injection, a markedly dilated superior vena cava is usually demonstrated. The right auricle and right ventricle are markedly enlarged; there is dense premature filling of the left auricle from the auricular septal defect. The left heart chambers are usually markedly hypoplastic and as a result are often poorly visualized. The dilated pulmonary artery and small aorta fill simultaneously. The peripheral pulmonary artery branches are markedly increased in caliber. When the pulmonary veins become opacified, those on the right side cross behind the heart converging with those on the left to form an anomalous dilated "left vertical vein" which enters the left innominate vein. Immediately after opacification of the pulmonary veins, there is definite opacification of the left innominate vein and re-opacification of the superior vena cava and right chambers. Often, in the initial films, there is a filling defect in the column of the contrast medium in the superior vena cava produced by sudden dilution from the blood from the left innominate[133]. In total anomalies of the pulmonary venous return, the left chambers are never opacified to a greater degree than the right chambers, thereby differentiating from atrial septal defect and partial anomalous venous return.

2. Total anomaly of the pulmonary venous return into the right auricle. As yet, no angiocardiographic descriptions have been encountered.

B. PARTIAL ANOMALIES OF THE PULMONARY VENOUS RETURN. It has been stated[186] that partial anomalies are of functional significance only if more

than 50% of the blood flows through the anomalous channels into the right side of the heart. The majority of cases which have been seen have been incidental findings in asymptomatic patients; occasionally a partial anomaly is associated with a large auricular septal defect.

1. Partial anomaly into the inferior vena cava. Several angiocardiographic descriptions of this anomaly have been reported[55,91,196]. In most cases the diagnosis can be made from the plain chest film: a bizarre, dilated vascular channel is seen running obliquely downward and medially in the right lung field to the region of the inferior vena cava; there is usually a shift of the heart toward the side of the anomalous vessel. The dilated vessel becomes opacified on angiocardiogram with the filling of the pulmonary veins, and following this there may be re-opacification of the inferior vena cava and right chambers.

2. Partial anomalous pulmonary venous return into the superior vena cava. This anomaly has been demonstrated by selective angiocardiography with the catheter in the anomalous vessel[203]. In the initial films, there is sometimes a localized filling defect in the dye column in the superior vena cava at the site of insertion of the anomalous vein. In the later films, the anomalous channel becomes opacified with the pulmonary veins and there may be re-opacification of the right chambers.

3. Partial anomaly of the pulmonary venous return into the right auricle. This anomaly may occasionally be diagnosed on plain chest films and occassionally by angiocardiography; when the anomaly is present on the right side, in the early films there may be a filling defect or "turbulence effect" in the lateral portion of the right auricle; sometimes the anomalous veins will opacify somewhat earlier than the pulmonary veins of the opposite side; sometimes they are irregular in contour and abnormally dilated. From observations of cases of the tetralogy of Fallot which have been operated on, it is well established that many partial anomalies of the pulmonary venous return into either the venae cavae or right auricle are invisible on pre-operative angiocardiograms[41]. Partial anomalies are not infrequently demonstrated by cardiac catheterization and not seen on angiocardiogram. It has rarely been possible to reverse the blood flow in the right heart by forceful injection and obtain retrograde filling of the anomalous veins.

Anomalies of Venae Cavae. Isolated anomalies of the venae cavae are uncommon, but occur incidentally in 3% of congenital cardiovascular lesions[104]. Most of these anomalies are of no functional importance.

1. PERSISTENT LEFT SUPERIOR VENA CAVA. These are demonstrated angiocardiographically only if the injection is made into the left arm[157,174]. Uncommonly, the left superior vena cava may insert into the left auricle, and this is of considerable functional importance. The abnormal early filling of the left auricle from the left superior vena cava can be demonstrated by angiocardiogram[157]. The right auricle may fill from the left auricle through an auricular septal defect[189]. The left superior vena cava more commonly empties by way of the coronary sinus into the right auricle[47,174]; it may occur singly or the right superior vena cava may persist. There is usually no intercommunication between a double superior vena cava[190] but sometimes a communicating hypoplastic left innominate vein is demonstrated. Occasionally, the left superior vena cava is rudimentary or hypoplastic and the main flow is through the left innominate into the right superior vena cava.

2. CONGENITAL ABSENCE OF THE IN-

FERIOR VENA CAVA[63,189]. This rare anomaly is well demonstrated by angiocardiography done by a saphenous vein injection; the contrast medium will fail to show any inferior vena cava in the normal position. In the lateral views, dilated veins posterior to the heart become opacified, extending forward and entering the right auricle. This anomalous drainage may be either by way of an azygos vein[63] or a persistent right posterior cardinal vein[189]. The anomaly is often associated with a persistence of the left superior vena cava.

3. ANOMALOUS INSERTION OF THE INFERIOR VENA CAVA. The upper portion of the inferior vena cava not uncommonly opens into the posterior aspect of the superior vena cava rather than into the right auricle[127].

4. ANOMALOUS LEFT INNOMINATE VEIN. Rarely the left innominate vein passes beneath the aortic arch and the left pulmonary artery to enter a right-sided superior vena cava[174].

Congenital Pulmonary Arteriovenous Fistula. 1. DEMONSTRATION OF THE ABNORMAL VASCULAR CHANNELS IN THE LUNGS. Plain films of the chest almost always show some abnormality in the lung field, such as rounded or lobulated densities with cord-like strands radiating from the adjacent hilum to the lesion. Tomograms of the lung also reveal the nature of the lesion quite well. Nevertheless, congenital pulmonary arteriovenous aneurysm is one of the few conditions in which angiocardiography is mandatory prior to surgical attack, because it is the most definitive procedure for determining the true extent and multiplicity of the lesion. Small multiple lesions are sometimes demonstrated which were clinically unsuspected, and not visible in plain roentgenograms[9]. Occasionally a lesion is solitary and limited to a single segment of one lobe[175]. Excellent visualization of the lesions can be achieved by selective angiocardiography with the catheter in the pulmonary artery[113], but in a majority of cases satisfactory demonstration can be obtained with the intravenous method. There is usually almost simultaneous opacification of the dilated pulmonary artery branches supplying the lesion, the irregular fistulous channels, and dilated veins draining the area.

From a review of the literature up to 1952 by Sloan[185] (a group of 85 cases), the lesions were found to involve more than one lobe in 30% and both lungs in about 25% of cases. The lesions are slightly more common in the right lung and somewhat more common in the lower than in the upper or middle lobes. Thirty of the 85 cases had angiocardiography, and in all of these except one, the nature of the lesion was demonstrated. In one case a congenital arteriovenous fistula was strongly suspected clinically, but was not demonstrated by angiocardiography[13]. It is theoretically possible that very small arteriovenous fistulas with only fine vessels may not be visible on angiocardiography. In one unusual case[185], a regular chest Roentgen-ray examination was completely negative, but angiocardiography revealed a direct shunt between the right pulmonary artery and left auricle.

2. CHANGES IN THE HEART AND GREAT VESSELS. Although the cardiac output is often normal, from 10 to 20% of the cases[185] have enlargement of the cardiac chambers which cannot be explained by other causes. The pulmonary vascular tree elsewhere in the lung often opacifies poorly, or later than the involved areas. The increased rapidity of the circulation is usually demonstrated by abnormally early opacification of the left chambers.

Anomalies of Cardiac Position. Many different types and classifications of the positional anomalies[104,191] are described

in the literature. In the straightforward types, such as dextroposition of the heart secondary to pulmonary lesions and asymptomatic "mirror image" dextrocardia with or without abdominal situs inversus, the diagnosis can be adequately made on the plain chest film. In the dextrocardias complicated by additional anomalies, however, angiocardiography is the ideal method for demonstrating the arrangement of the cardiac chambers and the direction of the blood flow[18,87,104,191,215]. The degree of cardiac rotation can also be assessed. In these complicated dextrocardias, considerable confusion results if the terms "right" and "left" are used in naming the cardiac chambers; it is preferable to use the terms "anterior" and "posterior" in describing the chambers[215]. In cases of levocardia with abdominal situs inversus, angiocardiography is of value in demonstrating the additional anomalies which commonly occur, such as right aortic arch, anomalies of the superior vena cava and pulmonary veins, transposition or overriding of the aorta, and pulmonic stenosis[215].

Single Ventricle. This anomaly is often difficult to diagnose by clinical means. Although angiocardiography may prove very useful in its diagnosis, only a few scattered cases have been found in the literature[126,148]. There are a great many variations in this anomaly, and it is often commonly associated with other anomalies such as pulmonic stenosis, transposition, the tetralogy of Fallot, and truncus arteriosus. Sometimes there is only a single ventricle anatomically. At other times, however, two ventricles may be present, one being enlarged and the other rudimentary. Sometimes the large ventricle gives rise to both great vessels, the rudimentary chamber receiving its blood only through a ventricular septal defect. More frequently, one or both great vessels arise from the rudimentary ventricle.

On angiocardiogram, the diagnosis may be made by immediate and total filling of the entire ventricular area[126] in rapid serial films. Sometimes it is difficult or impossible to determine on angiocardiogram the difference between single ventricle and a very large ventricular septal defect but the functional effect of these anomalies is very similar. Occasionally, the rudimentary ventricle if present may be opacified and visualized. The rudimentary chamber is often located in the left side of the heart in the region normally occupied by the infundibulum. When the pulmonary artery arises from the rudimentary chamber there is often a functional pulmonic stenosis and decreased peripheral vascularity. When the aorta arises from the rudimentary chamber its origin in the A.P. views is often seen far to the left of the mid-line, forming a large curved contour in the left upper mediastinum.

Aortico-pulmonary Septal Defects. The correct diagnosis of this lesion is important, as it is now amenable to surgery. The condition is usually impossible to tell clinically and in regular chest film and fluoroscopy from a patent ductus arteriosus; almost all of the cases in the literature[81] have been diagnosed either at surgery or necropsy. Only rarely is it possible to insert a cardiac catheter from the base of the pulmonary artery through the defect into the aorta.

1. ANGIOCARDIOGRAPHIC FINDINGS USUALLY IDENTICAL WITH PATENT DUCTUS ARTERIOSUS. Enlargement of the left chambers, dilatation of the pulmonary artery and its branches, continued opacification or re-opacification of the pulmonary artery at the time of the aortic filling[84], are usually indistinguishable from patent ductus arteriosus. The infundibulum of the descend-

ing aorta which is sometimes present in patent ductus will not be present, but this is of no help in differentiation, as it is not always present in patent ductus. Poor opacification of the pulmonary artery branches has been observed with good opacification of the main pulmonary artery, due to the sudden dilution of the contrast medium by the systemic blood flowing through the septal defect[130].

2. DEMONSTRATION OF THE SEPTAL DEFECT BY RETROGRADE AORTOGRAPHY. Gasul, Fell, and Casas[81] first demonstrated the defect during life and differentiated the lesion from patent ductus arteriosus by retrograde aortography. In the left oblique view, a stream of the contrast medium was seen extending from the base of the aorta a short distance above the semilunar valves into the main pulmonary artery.

Unilateral Atresia or Absence of Pulmonary Artery. Although this anomaly may be suspected by a complete absence of pulmonary artery shadows in one lung in plain chest films, it is best diagnosed by angiocardiography[107,140,153,214]. Rarely, the anomaly may be isolated[214]; usually it is associated with other cardiac anomalies. Some degree of unilateral hypoplasia of the pulmonary arteries is common in the tetralogy of Fallot, but only about 1 to 2% have unilateral pulmonary artery atresia[153]. The congenital absence usually involves the right main branch[124], but in the tetralogy of Fallot, it usually involves the left[153].

On angiocardiography an enlarged main pulmonary artery is demonstrated with only one branch, the other branch being completely absent. In the later films with opacification of the aorta there may be lace-like strands on the side of the atresia due to dilated bronchial arteries. There is usually a shift of the heart toward the side of the atresia. In many cases, the remaining branch of the pulmonary artery becomes markedly dilated and may cause bronchial obstruction[153]. A unilateral atresia is an invariable accompaniment of aplasia of the lung; in these cases, angiocardiography may be of value in differentiating pulmonary hypoplasia from aplasia[107]. There is marked displacement and rotation of the heart toward the side of the aplasia.

Persistent Atrio-ventricularis Communis. In the few cases in the literature that have had angiocardiography[82,87,125], none has shown the direct visualization of the auricular and ventricular septal defect immediately above and immediately below the tricuspid and mitral valves. The predominant shunts through the defects are usually from left to right; nevertheless on several angiocardiograms there has been a rapid simultaneous filling of all four chambers and simultaneous filling of the aorta and enlarged pulmonary arteries. This unusual angiocardiographic finding should suggest the diagnosis[82,87]. The right chambers are enlarged, the main pulmonary artery is dilated and usually of larger caliber than the aorta; the peripheral pulmonary artery branches are prominent. In some cases reported in the literature, however[125] there has been no reversal of the shunt and no premature filling of the left chambers; then the angocardiogram shows only nonspecific prolonged or re-opacification of the right chambers.

Congenital Stenosis of Mitral and Aortic Valves. In congenital mitral stenosis, enlargement of the left atrium often occurs, but this usually can be demonstrated by routine roentgenographic procedures. There is often prolonged opacificaton of the left auricle due to generalized slowing of the circulation. In rapid serial angiocardiograms[208], the left auricle contains a

greater amount of residual contrast medium than normally at the end of atrial systole. When there is no definite enlargement of the left atrium, the presence of a mitral stenosis will not be demonstrated[6a].

Some authors state that it has never been possible to visualize a sub-aortic or aortic stenosis by angiocardiogram[113]. There is only one angiocardiographic demonstration of a sub-aortic narrowing in the literature[96] and this case is not proven. The outflow tract of the left ventricle is probably the most difficult area in the heart to demonstrate by contrast methods[194]. Although the stenosis itself cannot be demonstrated, the enlargement of the left ventricle and post-stenotic dilatation of the ascending aorta may be seen[104].

Miscellaneous Anomalies of the Aorta. One case of congenital aneurysm of the right sinus of Valsalva was diagnosed successfully before rupture by aortography in the right oblique projection, as an abnormal projection of the contrast medium beyond the right aortic sinus[71]. A surgically proven rupture of a sinus of Valsalva into the pulmonary artery was demonstrated by thoracic aortography[114]. A congenital aneurysmal dilatation of the ascending aorta was demonstrated by angiocardiogram in a case of arachnodactyly[179]; there was also a filling defect in the lateral wall of the aorta thought to be due to thrombus.

Cardiac Arrhythmias Associated with Congenital Lesions. In rapid serial angiocardiography[99,208], complete heart block is demonstrated by a complete independence of the atrial and ventricular systolic and diastolic phases. Some of the films will show auricular and ventricular systole occurring simultaneously. Auricular fibrillation is easily detected by a complete absence of change in the size or shape of the auricles in serial films.

Congenital Cardiac Aneurysm. A case of congenital aneurysm of the right ventricle was demonstrated as an outpouching of the contrast medium in the left oblique projection[149].

Endocardial Fibroelastosis. Only a few cases with this anomaly have been studied angiocardiographically[82]. The heart is markedly enlarged, and usually the dilatation of the left chambers is much more marked than the right. The pulmonary vascularity is usually normal and no shunts are demonstrated. The circulation time is usually extremely slow, with prolonged opacification of the left chambers. In the left oblique view, the marked thickening of the left ventricular wall may be demonstrated; in rapid serial films poor contraction of the left ventricle may be shown with very little difference in the size of the heart in systole and diastole. It is theoretically possible that anomalous left coronary arteries may become opacified with filling of the pulmonary artery in early films, but as yet this has not been observed. In the lateral projection, there may be marked forward displacement of the interatrial and interventricular septa with extreme narrowing of the right auricle and right ventricle, due to the tremendous enlargement of the left chambers. Deformities of the mitral and aortic valves are common, but this cannot usually be determined by angiocardiography.

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DERMATOLOGY AND SYPHILOLOGY

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PIGMENTED NEVI AND MALIGNANT MELANOMA OF THE SKIN
A SURVEY OF SOME OF THE RECENT LITERATURE

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TREATMENT. CERTAIN PRINCIPLES. *Type.* This review will be confined to the treatment of junction nevi.

Location. Since nevi occurring on the palms, soles and genitalia are nearly always junctional in type, their prophylactic removal should be advised. Sites of chronic irritation, such as the face in a person who shaves over a nevus, the belt line, and the like, deserve similar consideration.

Size. The size of a pigmented nevus bears no relation to its malignant potentiality, and indeed the small percentage of malignant melanoma that arise *de novo*, by expressing themselves as metastatic lymphatic lesions, might indicate that there had been microscopic malignant change in the primary lesion. The latter might be a tiny junction nevus, that had not even been noticed, or as Allen and Spitz[4b] have pointed out, a minute area of junctional change in a nevus, which was causing no symptoms.

Ulceration. This sign should indicate the probability of malignancy. Certainly as Allen and Spitz[4a] indicate, it provides a pathway towards dermal dissemination, as well as to surface breakdown.

Margins of Excision. The suggested safe margin of excision varies a great deal, from the wide surgical zone down to the margins of an excision biopsy. Sachs *et al.*[96] say that all that need be removed is the junction nevus itself.

Hormonal Factors. Hormonal factors will be discussed later in this review. However, Pack and Scharnagel[82] and Cunningham[25] recommend that suspect junction nevi in children should be excised before the age of puberty. Similarly junction nevi in pregnant women should demand careful consideration.

Biopsy. One should insist on the necessity of obtaining a specimen satisfactory for histopathological examination. Dermatologists may pride themselves on their diagnostic acumen, but as Becker, Sr., and Swerdlow have statistically shown, their "batting average" is low enough to permit many tragic mistakes. The histopathological examination is available anywhere, and it is relatively inexpensive.

Dermatologists should consider the medicolegal aspects of the failure of having a histopathological report in the unfortunate event of ensuing malignancy following the removal of a nevus.

Modality. Only two modalities are widely used: surgical excision and electrosurgery with or without curettage. Of recent years, there has been a definite trend to adopt surgical excision exclusively. Certainly this method provides a satisfactory specimen for examination, and is least apt to disturb a restive tissue. Perhaps the reasons why more pigmented nevi are not so treated is by virtue of their size and number. Electrosurgery has the advantage of speed and easy handling especially for the smaller, multiple lesions, but depending on the type of procedure used, biopsy material may be either inadequate or unsuitable.

Other modalities such as carbon dioxide ice, plastic planing and sandpapering, and others, need not be considered further.

What nevi should be treated? Cunningham[25] has produced an excellent list in which "the surgical removal and histologic examination of the following lesions is recommended."

"1. All pigmented lesions on the soles of the feet, palms of the hands, and on the scrotum.
2. All ulcerated pigmented lesions.
3. Those pigmented lesions subject to chronic irritation by reason of their anatomic location.
4. Pigmented lesions with irregular borders, pigmented fingerlike

projections, or with accompanying satellitosis.

5. Any suspect nevi in children prior to puberty.
6. Any pigmented lesion on the genitals and feet, as well as those subject to irritation, of all pregnant women in the early prenatal period."

The reviewers would like to substitute the word genitalia for scrotum in number 1, and pregnancy for prenatal in number 6.

CERTAIN RECOMMENDATIONS. *S. William Becker, Sr.*[7c]. Becker, Sr., adopts a conservative approach. For a suspected lentigo maligna, surgical excision is advised, whereas for macular nevi, papular nevi, electrosurgery is used.

G. M. Lewis[62]. "A lesion considered to be a junctional nevus and showing increased activity should be promptly excised. Lesions having the clinical features of junctional nevi should never be treated by electrolysis, solid carbon dioxide, electrodesiccation or acids."

H. Montgomery[71a]. "Eradication of moles is essentially surgical. Moles should never be partially removed by electrolysis, carbon dioxide snow or superficial cautery, because the nevus cells penetrate deeper into the cutis. Even in the nonjunction type of lesion, if removal is not complete, scar tissue may act as an irritant to the nevus cells and malignant melanoma may eventuate."

Sachs, MacKee, Schwartz and Pierson[96]. These authors recommend that junction nevi should be excised, and that all that is required to be removed is the nevus itself.

Traub[111]. "Junction nevi on the feet and on other body areas where they may be exposed to varying degrees of more or less constant trauma should be prophylactically removed. Also any junction nevus that appears suddenly in adult life and continues to grow, should be excised."

Frank[41]. "We must, therefore, conclude that each case is an individual problem, and, in the present state of our knowledge, the results obtained will depend to a large extent on the clinical judgment and experience of the individual physician."

Shaffer[99]. "If there is any doubt, therefore, with the diagnosis of pigmented lesions, they should be excised for histologic examination and for pathologic differential diagnosis. When a pigmented nevus is to be removed, if at all possible, it should be excised surgically *in toto* with a rim of normal skin around it. The excision should extend through the skin into the panniculus. All pigmented nevi upon excision should be biopsied."

Beerman[9]. Beerman states that surgical excision is the method of choice for the treatment of pigmented nevi. Partial removal by superficial fulguration, electrolysis, solid carbon dioxide or caustics can result in the development of malignant melanoma in a small percentage of cases. There is no place for Roentgen-ray therapy or radium in the treatment of nevi.

Ekbald (*Ekbald, G. H.*, A.M.A. Arch. Dermat. & Syph., **70**, 399, 1954) reviewed 30 opinions on the therapy of benign nevi in the literature and concluded that conservative therapy of intradermal nevi is safe if biopsy is done and that junction-type nevi should be treated so as to insure removal or destruction of all nevus cells.

Chapman and Klopp (*Chapman, D., and Klopp, C. T.*, Med. Ann. Dist. Columbia, **23**, 308, 1954) favor surgical excision for all pigmented skin lesions.

Summary. The Schoch Letter for March, 1951[98], posed the following question to 50 prominent dermatologists, "When you advise removal of simple pigmented or nonpigmented

nevi, do you in most instances advise: 1) Surgical excision? 2) Electrosurgery with or without curettage? 3) Simple curettage followed by a hemostatic?" Seven dermatologists checked number 1, surgical excision. Forty men checked number 2, electrosurgery, and 3 said both procedures were used equally.

Shaw[100] canvassed 201 dermatologists with the following answers. Only 7% used surgical excision at least 90% of the time; 70% used nonsurgical methods at least 90% of the time.

It would appear, therefore, that the modern trend towards surgical excision as the exclusive method of treating pigmented nevi is not generally accepted by the speciality. However, surgical excision is the method of choice recommended by these reviewers.

MALIGNANT MELANOMA. ETIOLOGY. *Incidence.* Clark and MacDonald[21] report that in an area of Texas during the period of 1944 to 1948 there were 20,000 cases of cancer, of which 298 were malignant melanoma, a rate of 1.5% of total cancer. MacDonald[65] reports that in the state of Connecticut during the period 1935 to 1946 the rate was 0.93% of total cancer, or an average incidence of 1.8 per 100,000. Ackerman[1] gives a figure of 2.9% of total cancer. For the Stockholm area, Sylvén states that malignant melanoma consists of 7.0% of total epitheliomas of the skin[109].

Location. The incidence of malignant melanoma according to location has been determined in two very large American series[4a,85b] with very similar results, and the larger of these[85b] will be presented in tabular form. In his discussion, Pack mentions that the figures for the head and neck (22.1%) and the sole of the foot (9.0%) are proportionately higher than statistically expected on the basis of relative skin area estimations. Decker and Chamness, in 1951, reported a series of 25 cases occurring on the plantar surface of the foot, including a high Negro incidence in that area[28].

TABLE 8.[85b]—INCIDENCE OF MELANOMA ACCORDING TO LOCATION 1917–1950.

Location	*Number*	*Per Cent*
Total Cases	1190	100.0
Head and Neck	263	22.1
Eye	56	4.7
Oronasal, esophagus	21	1.8
Arm	101	8.5
Palm	16	1.3
Subungual	35	2.9
Leg	218	18.3
Sole	107	9.0
Trunk	288	24.2
Genitalia	37	3.1
Anorectal	19	1.6
Primary Site Unknown	29	2.4

Age. McWhorter and Woolner[69,69a] have surveyed the world literature up to 1954 on the occurrence of malignant melanoma in children. Out of 102 cases that have been reported, there were only 18 which satisfied their criteria, insofar as sufficient information for review was concerned. Excluded, of course, were the juvenile melanomas, as well as the cases of transplacental transmission of malignant melanoma from mother to child[27,51,116]. These 18 cases, 5 each from two large centers, are analyzed and the results presented in tabular form. An excellent discussion of juvenile melanoma is given. In a later report, McWhorter, Figi and Woolner[69a] noted that 6 to 8% of all pigmented nevi removed surgically from children were juvenile melanomas. They also occur in adults. Allen and Spitz[4a] estimate the incidence of malignant melanoma in children to be 0.3% of all malignant melanoma of skin and mucous membranes. Williams, in 1954, reported the most recent case, in which fatal metastases occurred in

a 5-year-old girl. The lesion had resulted from malignant degeneration of a giant hairy mole, which had been present since birth, and which covered symmetrically practically all of the trunk and arms[122].

Allen and Spitz[4a] state that 62.7% of malignant melanoma in their series occurred between the ages of 31 and 60 years. This has been generally confirmed[84,124].

With regard to the correlation between survival rates and age, Pack[85b] has shown that there is no difference in the postpubertal age groups of 11 to 30 years of age, and the older group, of over 30 years.

Sex. It has been generally thought that the disease seemed to be equally distributed among the sexes[4a,65,85,124]. However, Wright, Clark and Milne in their series reported in 1953 discovered a preponderance of females at all ages and sites[125].

Race. It was thought for a long time that malignant melanoma was rare in the Negro race. However, recent information reveals that it is not as unusual as previously considered. Morris and Horn[75] collected a series of 9 cases occurring in Negroes, during the period of 1940 to 1951, at the Hospital of the University of Pennsylvania. During this same time, there had been 104 cases in white people. When the relative population figures for the white and Negro races in hospital admissions was compared, the rate was 4.4 times greater. In these cases, 6 occurred on the foot and one on the leg, again demonstrating the predilection for those areas in the Negro. The authors mention that there have been 430 cases of malignant melanoma occurring in the African and American Negroes.

Allen and Spitz[4a] estimate an equivalent incidence of 3.7 to 1, whereas Imler and Underwood say 3 to 4 to 1[55].

Baxter[6] pointed out that the incidence was higher in the African Negro than in the American Negro. He also gave a race location difference in that 65.3% of 170 cases of malignant melanoma in the Negro race occurred on the feet. This has also been observed by DesLigneris[29] and Hewer[50]. They considered the practice of going barefoot, with the subsequent frequency of trauma from thorns and sharp stones, constituted an etiological factor in the African Negro. Cunningham[25] mentions that the disease occurs more commonly in the more lightly pigmented areas, such as the soles of the feet, the nail bed and the oral mucosa. Baxter[6] suggests that it is prone to occur in areas where there was a change from dark to light pigmentation.

Genetic. In a learned paper, Cawley[18] shows that heredity plays a definite role in malignant melanoma in fishes and in animals. He speaks of Gordon's work[45] in this field. There is evidence to suggest that castration in swine protects against metastases. Such indication of the efficacy of hormonal influences in humans has been disappointing. Another point of interest is that gray horses are extremely susceptible to inherited malignant melanoma, with the conclusion that skin color and malignant melanoma may be controlled by very closely related genes. Malignant melanoma only occurs rarely in other animals. Cawley then mentions several cases from the literature, which seem to have hereditary factors, although none of these was malignant melanoma of the skin. The author then presents 3 cases of malignant melanoma occurring in one family, in which there is presumptive evidence to indicate a common genetic background.

Pre-existing Nevi. This subject has come up repeatedly in the section on pigmented nevi. It will be sufficient here to say that according to Cunningham[25] the figure of 56.9% which repre-

sents the average of 5 clinical series, totalling 1219 cases, is the proportion of malignant melanomas believed to have arisen from a pre-existing mole[2,26,32,81,123].

Skin Color (Complexion). Clark and MacDonald[21] in their Texas Registry studies, have shown that the incidence of malignant melanoma of the head and neck is significantly lower (20.8%) in Texas than the average of 5 other series (25.1%), despite the known intensity of the Texas sun. This piece of statistical evidence contradicts previously held opinion on the relationship of actinic rays to skin cancer.

Pack[79b] states his opinion that "it may be stated arbitrarily that malignant melanomas occur relatively more frequently in blond individuals, particularly those people who have extremely pale skin, often translucent and of soft texture, and including those of sandy complexion who may freckle easily but do not tan well or heavily on exposure to sunlight. Such people do not seem to have a well-developed resistance to the growth of pigmented tumor cells."

Hormonal Influence. The role that certain unknown factors, presumably hormonal, play in melanogenesis in childhood, at puberty and during pregnancy has already been discussed. That a pituitary-adrenal axis may play a regulating role in the hyperpituitarism, such as seen in pregnancy, Addison's disease and acromegaly, has recently been discussed by Fitzpatrick and Lerner[38,59]. This was first discovered when hyperpigmentation was seen to occur following the administration of corticotropin for arthritis. Recently also Lerner, Shizume and Fitzpatrick have determined that the active principle was the melanocyte-stimulating hormone (MSH). Further study has indicated that two factors appear finally to establish MSH as an important part of the control of human melanin formation. These are: "the demonstration of MSH activity in the urine in various conditions, known to be associated with increased pigmentation, such as Addison's disease and pregnancy[60], and the production of generalized melanin hyperpigmentation in humans following administration of MSH"[101].

Xeroderma Pigmentosum. As mentioned by Allen[4a] and also earlier in this review, the incidence of malignant melanoma occurring in cases of xeroderma pigmentosum is about 3%, which is very much higher than in the general population, where the incidence is in the order of 0.018%.

Moore and Iverson, in 1954, have reviewed the literature in this field and present a patient with xeroderma pigmentosum, who had, at different times over a period of 30 years, developed over 20 basal cell epitheliomas, one squamous cell carcinoma, and finally one malignant melanoma of the skin. This brings the number of cases of xeroderma pigmentosum with this complication in the literature to 9, giving an incidence of 3%, since there are 360 of the latter disease in the world literature[74].

Van Patter and Drummond[115] have described the case of a woman who had suffered from 7 histologically proven skin cancers and who had survived 8 years following the diagnosis of the first of her three malignant melanomas.

Trauma. The relatively high incidence of malignant melanoma on the leg and especially the foot in the white race, and the much higher incidence in the Negro, especially the African Negro, has provoked much thought about the role of trauma. Some of this was alluded to in the section on race. Allen[4a] contributes his views to this enigma by referring to 3 cases of malignant melanoma occurring in burn scars,

3 in irradiated areas and one following sunburn.

DIAGNOSIS. ACCURACY. The tables previously shown dealing with the accuracy of diagnosis of pigmented nevi will be used to illustrate the same features in malignant melanoma. Becker, Sr.[7c] in his series shows that the clinical diagnosis was confirmed by microscopic means in 43%, whereas with the specimens that had been diagnosed histopathologically, the clinical diagnosis had been made in 48%. Swerdlow[108] gives equivalent figures of 28% and 59% respectively. As Becker, Sr., also mentions the diagnosis of amelanotic malignant melanoma is practically never made clinically.

DIFFERENTIAL DIAGNOSIS (Clinical). The following list of relatively common lesions should be considered:

1. Pigmented nevus.
2. Seborrheic keratosis.
3. Granuloma pyogenicum.
4. Pigmented basal cell epithelioma.
5. Pigmented squamous cell carcinoma.
6. Histiocytoma (sclerosing angioma).
7. Blue nevus.

Of lesser importance are the following: verruca vulgaris, fibroma, sebaceous cyst, keratoacanthoma, glomus tumor, angiokeratoma and Kaposi's sarcoma. Attention should also be paid to the possibility of cutaneous or subcutaneous hemorrhage, as pointed out by Goldman[44].

AIDS TO DIAGNOSIS. *a*) With pre-existing mole. *Pigmentation.* Sudden darkening, or increase in pigmentation of a mole is a serious omen. Although this can occur in the absence of malignant change, such as in pregnancy, or exposure to sunlight, it must be regarded with high suspicion. The change in color is usually from brown to brownish black or to black, although any other change may also be significant.

The deeper pigmentation change need not be uniform over the whole mole, but may occur as a darker spot in a central or in a circumferential area.

Small, darkly pigmented nodules may appear about the periphery of the mole, giving a "sooty-like halo"[2]. This so-called "satellitosis"[25] is very suggestive of malignant change.

Since mucous membrane lesions of malignant melanoma are frequently not pigmented, failure to realize this fact may serve to delay the diagnosis[4a].

Size. Increase in size of a mole may result in it becoming raised above the surface of the skin, or it may extend radially. In either case, any activity of the lesion is to be suspected. Such increase in size may be reflected in surrounding induration.

Ulceration of Surface. This sign, occurring in a mole, usually indicates malignant degeneration. Here the histopathological correlation is very clear, and as Allen and Spitz have vividly described[4a] such a process is possible by the lack of cohesiveness of the malignant cells, with spontaneous acantholysis of the epidermis. The larger a surface, the more apt is ulceration to occur. Tompkins, in 1953, states, "As a single prognostic sign, ulceration was found to apply regardless of site of origin or sex of patient but it was related to size of tumor." Surface bleeding has much the same significance as ulceration. Exuding of serum, which turns black on exposure, has also been reported[110].

Irritation. Irritation of a lesion, in the process of undergoing malignant change, is an occasional symptom, the basis for which does not seem clear.

Metastases. In approximately 10% of cases, lymphatic metastases may be the presenting sign of malignant melanoma.

Location. Certain locations of an unusual lesion, such as one on the soles,

or the palms or under the finger nail should arouse suspicion.

b) Without pre-existing mole. Becker, Sr.[7g], states that "Melanoma originates in pigmented nevi in 25% of instances. It originates as lentigo maligna in 75% of cases." The same author then goes on to describe the clinical appearance of the latter lesion[7h], "The first clinical sign of melanoma is in the form of a dark brown maculo-papule on the skin, lentigo maligna, or melanoplakia, usually blackish on the mucosa. Lentigo maligna slowly enlarges and, after a few months or years, it becomes elevated, oozes serum or bleeds easily, or both, and, eventually, an elevated tumor appears, which may be pigmented in a shade varying from brown to black, or may be nonpigmented and erythematous." As he further points out[7h], it may be regarded as a "melanoma *in situ* or as a premelanomatous lesion." It becomes truly malignant as soon as it penetrates into the dermis.

c) SPECIAL MEASURES. *Biopsy.* There has been considerable difference of opinion as to the danger of performing a biopsy upon a malignant melanoma, because of the fear that such a procedure, by opening up venous and lymphatic channels, may permit the immediate dissemination of the disease. Although there have not been any instances of this accident recorded, and although many experienced clinicians feel that the widespread concern is unwarranted, nevertheless the fear of such a tragedy persists. Therefore it is the opinion of the reviewers that the least procedure should be an excision biopsy, including a margin of skin about the lesion. Such an operation can be followed by wide local excision as soon as a confirmatory diagnosis is given. If, however, the lesion is highly suspected, it is recommended that wide local excision, with dissection of the subcutaneous tissues and fasciae, be carried out with a skin margin of 5 cm. Such an excision will, of course, require an immediate skin graft. Because of the relative inaccuracy of chemical diagnosis, however, destructive and mutilating surgery should not be performed without histopathological confirmation by a preceding biopsy.

Melanosis and Melanuria. Lorincz[63] explains the phenomenon of melanosis and melanuria as follows, "Melanuria comes about because extensive melanotic tumors produce such great amounts of tyrosine oxidation products that some of them, like 5, 6-dihydroxyindole spill over into the general circulation and are excreted into the urine. Occasionally the circulating oxidation products of tyrosine may be oxidized to melanin in other tissues and thus account for the generalized intense melanosis that sometimes occurs." The use of Herter's and Thormählen's tests for indole can be used to identify qualitatively the urinary melanogens[63]. Several cases of extreme melanosis have been described, including a much quoted one by Dixon[30], and others by Odel, Montgomery and Horton[77] and by Pack and Scharnagel[82]. A recent article by Fitzpatrick, Montgomery and Lerner, entitled "Pathogenesis of Generalized Dermal Pigmentation Secondary to Malignant Melanoma and Melanuria" reviews this phenomenon, and in it is included a fine classification of dermal pigmentation[39].

Tyrosinase Reaction. The presence of an active or uninhibited tyrosinase system seems to be a characteristic of the malignant pigment cell. That the demonstration of such a system could be a means of diagnosing malignant melanoma from junctional nevi, or amelanotic malignant melanoma from other malignant tumors, has been proposed by Fitzpatrick[36]. The technique concerned seems relatively simple and consists of incubating slices of tissue in

tyrosine with subsequent paraffin imbedding, sectioning and microscopic examination. Indeed the alteration in color can be seen in the gross specimen after incubating in tyrosine. Further work is being done to develop an efficient micro technique.

Masson's Silver Technique. The use of Masson's silver technique in differentiating pigmented epithelial tumors may occasionally be a useful procedure, as suggested by Lennox[58].

Reticulin Content. The usefulness of determining the reticulin content of malignant melanoma of the skin, as a means of indicating prognosis, as proposed by Wilder and Callander[121] for similar lesions of the eye, has not been confirmed by Wright, Clark and Milne[125], or by Ackerman[2].

Cytodiagnosis. The use of cytodiagnosis including tissue smears and imprints in malignant melanoma has been revived in recent years by Tzanck and his associates, their most recent contribution being in 1954[112]. Haber[46] gives a critical evaluation of the procedure and lists 5 possible advantages: "1) Where a quick preliminary diagnosis is requested. 2) If the patient refuses biopsy. 3) In very old people. 4) If there are no histological facilities available. 5) If the lesion is difficult of access (such as the corner of the eye, mouth, nostril etc.)." The technique is simple and quick, but requires expert knowledge of the variations of morphology of cells in preparations of this kind. In no way can it, or is it intended to, supplant standard histopathological examinations. Another recent article is by Wilson[123]. The photographs in all three papers are beautifully clear, indicating the lack of distortion obtained in cytology, which may be the worst fault of standard methods.

SPECIAL VARIETIES. *Subungual.* First reported by Hutchinson[53], in 1886, and called "Melanotic Whitlow," this disease variant has been completely described by Pack and Adair. Between 1917 and 1937, they had collected 16 cases in their series, or an incidence of 3.4% of total malignant melanoma. By 1950, a further 19 cases had been added, to give a total of 35 cases, or an incidence of 2.9%[80]. This lesion is twice as common on the foot as the hand. It is seen as a dark-brown or black fungating lesion, usually growing from beneath the nail plate, or commonly in the sulcus. An important sign is "the border of coal black color, which is nearly always present at the edge of the involved nail"[85b]. A lengthy differential diagnosis of this condition is given. It is possible that pigmented nevi of the nail matrix may be a precursor. However, only 5 cases have ever been reported, the latest by Noble, Ferrin and Merandino in 1952[76].

Multiple Primary Malignant Melanoma. Pack, Scharnagel and Hillyer[83] reported a series of 16 cases of multiple primary malignant melanoma and point out the following reasons why such a disease variant has not been more often recognized: "1) Melanoma is not a common cancer and the experience of most surgeons and dermatologists is usually limited to a few cases. 2) The incidence of multicentric melanomas in any series of patients with melanoma is relatively rare. 3) The curability of melanoma is so low and the life expectancy of the average patient so short that he may die before new primary melanomas have a chance to develop, be diagnosed and recorded as independent lesions. 4) An inexperienced pathologist might erroneously interpret a new pigmented skin tumor as a cutaneous metastasis from a previously excised melanoma." Furthermore the author points out, that since many malignant melanomas arise from pigmented nevi, why do we not have many more instances of multiple pri-

mary malignant melanomas? In their series of 1250 cases of malignant melanoma, only 16 (1.28%) showed evidence of multiple primary lesions. Although suggestive clinical evidence may be present, usually this diagnosis is only possible by histopathological examination. The revealing description of Allen[83] follows, "Frequently primary malignant melanomas are confused with metastatic foci, especially when the latter are near the surface of the skin or mucous membrane. The importance of the distinction is obvious. In almost all instances this distinction can be determined unequivocally by the presence or absence of junctional change in the epidermis or epithelium overlying the lesion. The exceptions to this rule are the exceedingly rare malignant blue nevi and those primary tumors in which the junctional alteration is obliterated by extensive ulceration. The criterion applies to malignant melanomas of both skin and mucous membranes. Contrariwise, in the metastatic foci in the cutis or submucosa, no junctional change is present even though the metastatic cells are directly apposed to the epidermis. In isolated instances, the metastatic cells may invade the dermis and thereby deceptively simulate the junctional change. However, with relatively little experience, these few cases may be easily distinguished from the true junctional change which generally begins in the basal layer and the immediately overlying layers of the epidermis. It need hardly be added that when multiple primary melanomas are present, this same criterion obtains in each of the lesions."

Juvenile Melanoma (Prepubertal). *Malignant Melanoma in Children.* These two variants have been reviewed elsewhere in this paper; the former in the section on Pigmented Nevi, and the latter under Age in the Malignant Melanoma section.

Pregnancy. "The pigmentary changes occurring in the skin of the face, nipple and abdomen of pregnant women is universally known but the darkening of existent nevi, although often known and commented upon by women during pregnancy, has not excited attention nor apprehension by physicians. The transformation of benign nevi to malignant melanomas, the rapidity of their growth, their early dissemination, and the low rate of curability during pregnancy has not been generally known." This statement by Pack and Scharnagel, in 1951[82], is taken from their paper, in which the authors discuss the policy of management of pigmented moles and malignant melanoma associated with pregnancy and give a list of recommendations summarizing their opinion. Hormonal therapy has been found to be of no value, nor is therapeutic abortion indicated. Cases of placental transmission from mother to child are reviewed. In their series of 1050 cases of malignant melanoma, there were 34 associated with pregnancy.

Mucous Membranes. Malignant melanoma of the mucous membranes, which includes that of the oropharynx, esophagus and anus[4a], has been excluded from this review.

HISTOPATHOLOGY. CLASSIFICATION. Malignant melanoma is generally divided into two groups, for histopathological purposes: 1) the superficial, or early; 2) the deep or advanced. Insofar as the first sign of malignant change in any malignant melanoma begins at the dermo-epidermal junction, whether or not the lesion originates from an active or precancerous junction nevus, or *de novo*, it can be seen that this division into two groups represents progression only. The reader is referred back to the discussion on junctional activity earlier in this paper, which forms the

basis for the development of further malignant changes.

Superficial Group. Allen and Spitz[4a] found, in their series of 362 cases of malignant melanoma reviewed histopathologically, that 33 or 9.1% were classified as superficial. As the same authors have mentioned, the cardinal distinction between this lesion and the active or precancerous junction nevus is the presence or absence of dermal invasion. "The ACTIVE or precancerous junctional nevus has one or more of the following features: 1) the general features of nuclear anaplasia such as hyperchromatism, increase in nuclear and nucleolar size, irregular nuclear vacuolization, and mitotic figures; 2) subepithelial inflammatory reaction consisting preponderantly of lymphocytes; and 3) cytoplasmic vacuolization and fine melanin pigmentation reaching to the uppermost layers, that is, to the stratum granulosum and stratum corneum"[4a]. Couperus and Rucker[24b] have expressed the view that such a description fits the diagnosis of an intraepidermal malignant melanoma, which is quite plausible, for that is exactly what an active or precancerous junction nevus is, as long as it remains within the epidermis. With the advent of malignant change, actual invasion of the corium takes place, perhaps only in one rete peg[24b]. There is a more prominent lymphocytic inflammatory infiltrate now, and this often extends laterally, well beyond the epidermal change. Mitotic figures are usually few in number, but are present. The amount of pigment present, both in macrophages and melanocytes, is usually prominent. Frequently there is considerable thickening of the epidermis, with fewer rete pegs than normally. Giant cells are often present but few in number. This then represents the development of a malignant melanoma from the junction nevus, accounting for approximately half the cases. The remainder arise *de novo* or from lentigo maligna. "The only difference between melanoma arising as lentigo maligna and that arising in a nevus is the presence of nevus cells in the latter"[7c].

Advanced Group. Evidence of considerable junctional activity can still be seen. The epidermis now shows marked disorganization, with large, oval or circular areas, in which the structure is quite loose, extending right up to the stratum corneum. These loose oval areas contain cells that are varied in size, with many that are large. They have large, hyperchromatic nuclei, and frequent mitotic figures, often bizarre in type. The occurrence of surface ulceration is easily understood with such rarefied structure. Pseudoepitheliomatous hyperplasia is frequently present, with seeding of cells into the corium. In the latter, the tumor cells are of two basic types, the cuboidal or epitheliod, and the fusiform, both of which are present in any one lesion, but one, usually the cuboidal, predominates. Couperus and Rucker state[24b] that, in their series, the ratio was 3% pure spindle cell (fusiform), 30% mixed spindle and epitheliod, and 57% predominantly epitheliod. With the latter case, an alveolar structure is apparent with the cells arranged in nevus cell nests. The fusiform cells tend to form a fibrous type of structure, called by Cunningham[25], fasciculate or sarcomatoid, and resembling a fibrosarcoma. Mitotic figures can readily be found, and also an occasional giant cell may be seen. The amount of pigment varies considerably and this seems to be directly related to the rate and direction of growth, often being absent in the peripheral parts of the tumor, as well as in the amelanotic variety. On rare occasions invasion of vascular or lymphatic channels may be seen. The in-

flammatory reaction is less intense than in the superficial type, and this has been spoken of as permitting further invasion, as the "corralling" action of the inflammatory process is lost.

Primary versus Metastatic Lesions. The presence of an intact epidermis, overlying the malignant melanoma lesion, is conclusive evidence that the latter is metastatic in origin[4a]. The reader is referred to the section on multiple primary malignant melanoma. Often too, the bordering inflammatory infiltrate is minimal in a metastatic lesion. The diagnosis of metastatic lesions in lymph nodes and in viscera can be a real problem, although the presence of melanin can be suggestive. However, "it should be pointed out here that all pigmented cells seen microscopically in lymph nodes do not represent metastatic melanoma. Hemosiderin- and melanin-laden macrophages are found in a wide variety of conditions and can mislead the unwary"[25]. The same author mentions that "Taylor and Nathanson showed in their study of melanomas with metastases that lymph node involvement occurred in 57% of the cases within a year, 70% within two years, and 83% within three years. Intra-ocular melanomas are notorious for delayed metastasis, but the cutaneous tumors also have a disquieting tendency to reappear in general dissemination years after apparent cure. Wilbur and Hartman point out that metastasis may show up after ten to thirty years."

DIFFERENTIAL DIAGNOSIS. Again it seems logical to refer to that excellent paper by Allen and Spitz, "Malignant Melanoma, A Clinicopathological Analysis of the Criteria for Diagnosis and Prognosis"[4a] and their differential diagnosis will be condensed. The diseases or changes are divided into two groups. The first includes those benign lesions or changes which may be mistaken for malignant melanoma: 1) Active junction nevus. 2) Intradermal nevus, which is nonencapsulated or extends into fat. 3) Intradermal nevus, with agglutination of cells. 4) Compression of dermal fibrocytes. 5) Juvenile melanomas. 6) Melanin-filled macrophages. 7) Mitotic figures in nevi of childhood. 8) Cellular blue nevi. 9) Pigmented seborrheic keratoses. 10) Sclerosing angiomas (histiocytomas). 11) Lipid histiocytoma. 12) Urticaria pigmentosum. 13) Lichen planus and acute lupus erythematosus. The second group includes those lesions for which primary malignant melanoma may be mistaken: 1) Anaplastic epidermoid carcinoma. 2) Basal cell epithelioma, both pigmented and nonpigmented. 3) Paget's disease, mammary and extramammary types. 4) Lichen planus. 5) Metastatic malignant melanoma. 6) Active junction nevi. 7) Sclerosing angiomas.

TREATMENT. INTRODUCTION. The fact that controversy may exist over a debatable subject often is quite healthy, for it encourages approach along different lines and avoids the supreme danger of medical thinking, a "one-track mind." The current situation as regards the treatment of malignant melanoma fits that picture perfectly. On one side are the conservatives, or perhaps one might call them the ultra-conservatives, chiefly composed of dermatologists and some surgeons. Their policy is to recommend local excision, and watchful waiting, a policy based in part upon tradition and upon the fact that there is some evidence that their end results compare favorably with other means. On the other hand, the school of radical surgery, whose champions are the specialized cancer surgeons, are convinced that the proper method is to attack malignant melanoma along the accepted lines of treatment for other malignant lesions.

If the two schools could present comparable results, it would be easy to

decide which method should be followed. However, such is not the case. The radical school of thought has assembled between 1917 and 1950 an outstanding series of 1190 cases, whereas the conservatives have formed their opinions from a collection of smaller studies, where the same standard conditions have not applied.

It seems wise, therefore, to warn the reader of these facts, and to remind him that, once the diagnosis of malignant melanoma is made, it becomes a surgical problem.

SURGICAL PROCEDURES. Cases with visceral or with inoperable lymph node metastases, which on occasions, might benefit from a palliative surgical operation will not be considered further.

The choice of surgical procedure depends largely upon two factors, the location of the lesion and the presence or absence of clinical lymph node metastases. The unpredictability of the latter can be shown by the statement of Raven[91] that 50% of the cases, where the lymph nodes were not enlarged clinically, showed microscopic evidence of tumor cells. However, a base line must be made somewhere. The cases will then be discussed according to the presence or absence of clinical lymph node metastases.

Without clinical lymph node spread. In this event, the wide local excision of the primary lesion is recommended. This consists of excision with a skin margin of at least 3 cm. on either side, plus removal of the subcutaneous tissue and fat, with further removal of the fascia underneath, to a wider degree than the surface skin excision. A skin graft will be required. Pack[91] does not routinely follow this procedure with prophylactic regional lymph node dissection, however Raven, Sylvén and Cunningham recommend that this be done[25,91,109].

With clinical lymph node spread. a) Where the lesion is situated close to the regional lymph nodes, wide local excision plus radical dissection, in continuity, of the regional lymph nodes is recommended. Examples would be any malignant melanoma, close to and draining into, the cervical, axillary and inguinal lymph nodes.

Surgical judgment may find it necessary to perform bilateral dissection, as for example of the inguinal nodes in the case of a lesion of the anus or genitalia.

b) Where the lesion is far removed from its draining nodes, depending upon location, there are two choices. The first is wide local excision, to be followed by radical dissection of the regional nodes. The question of a delay between the two stages of this operation cannot be given a definite answer. The rationale of such a delay is "to permit interception of lymphatic tumor emboli either already in transit or set free by the manipulation incidental to the operative procedure on the primary"[85b]. However, this delay has not been accepted by others[25] who feel that further dissemination from the nodes themselves might be permitted.

The alternative is radical amputation of an extremity, which is the procedure of choice recommended by Pack[85b] and Raven[91] for malignant melanomas on the foot or hand, with inguinal or axillary lymph node involvement. This operation, on the upper extremity, involves removal of the scapula, clavicle, the entire upper extremity, along with removal of the entire axilla and dissection of the lower cervical lymph nodes. This is the type of radical surgery that strikes trepidation both into the patient and into many physicians.

OTHER FORMS OF THERAPY. Roentgenray and radium therapy for malignant melanoma, in both man and animals, have proven disappointing. The disease

is notoriously radioresistant, and dosage levels exceed skin tolerance.

The use of radioactive isotopes has been limited and unsuccessful. Marcus and Rotblat have reported the experimental use of radioactive P_{32} in one case of malignant multiple melanomatosis, in which necrosis was produced both in the lesions and in the metastatic glands[66].

Hormonal therapy has also been useless. Pack and Scharnagel[82] stated that surgical castration, large doses of testosterone, pituitary gland irradiation, and even bilateral adrenalectomy had been without effect.

PROGNOSIS. THE PACK GROUP RESULTS. Pack, Scharnagel and Gerber, in their most recent analysis of their monumental study of 1190 cases, between 1917 and 1950, at the Memorial Center for Cancer and Allied Diseases, New York, report the following end results.

"1. A total of 1190 cases of malignant melanoma is reported covering a period from 1917 to 1950; 744 patients were seen up to 1946, of which 575 records are available for analysis. Of these 123 patients or 21.4% were free of evidence of melanoma five years or more, as of January 1, 1951. This incidence and the five-year results of melanoma according to anatomical location are presented."

"2. The five-year end results according to sex is 15.6% definitive cures for men and 27.4% for women."

"3. There is practically no difference in prognosis according to age after the onset of puberty."

"4. There were 73.3% of malignant melanomas in the operable group and delay in obtaining definitive surgery more than a month after adequate local excision reduced the five-year cures from 39.9% to 17.0%."

"5. The five-year end results according to type of surgical procedure are presented. The five-year end results in relation to metastases in regional lymph nodes are 14.1% for patients with nodes positive for metastases, and 40.5% for those with lymph nodes free of metastatic melanoma."

"6. The ten-year definitive cures of patients treated prior to 1940 were 9.2% (33 patients). Radical surgical treatment was routinely adopted after this date."

"7. The importance of obtaining proper surgical treatment of melanoma without delay cannot be overemphasized. The best chance for cure is at the time of first excision"[85a,b].

Location. Prognosis, as related to the location of the primary tumor, has much to do with lymphatic drainage and the subsequent effectiveness of surgery. Lesions of the trunk and anorectal regions, because of cross or alternate drainage, or both, have the lowest survival rates.

Sex. The disparity between survival rates and sex has been attributed to the "cancer consciousness" of the women as compared to the men. This has been pointed out by Pack *et al.*[85b] who state that at the Strang Clinic for Cancer Detection, the attendance of women is twice that of men.

Five-year Survivals. Since there has been some difference of opinion as to the validity of 5-year end results being accepted as a criterion of apparent cure, it should be pointed out that there does not seem to be any other satisfactory standard. Several cases are on record of long survival, or long delayed metastasis in malignant melanoma[23,43,49,94,120]. One case reported by Sumner in 1953, apparently the only one of its kind, indicates spontaneous regression of a malignant melanoma[107]. Such are the vagaries of the course of cancer and of malignant melanoma. Inevitably there will be exceptions to the rule, but the rule is only

made by compilation of a long series of well-documented cases.

OTHER SERIES. *Allen and Spitz*[4n] report a series of 123 cases, who were clinically free of disease for 5 years or longer following operation. Of these, local excision was carried out in 84 (68.3%) and local excision plus regional lymph node dissection in 39 (31.7%). Of the latter, the nodes contained metastases in 23, whereas 16 were free of disease. In 14 of the 123 patients subsequent local recurrences occurred, which were excised, and again the patients were clinically free for 5 years or longer.

Cunningham estimates a survival rate of from 30 to 40% in cases with negative nodes for the 5-year period, which figure drops to 5% with clinically positive regional nodes without distant metastases[25].

Weder and Watson in their series of 73 cases give equivalent figures of 44% five-year survivals with negative nodes, with 10% survival if the nodes were involved[117].

Clarke. This author suggests that "it is preferable to perform local excision and watch the patient for any enlargement of glands that may develop," feeling that nothing was to be gained by prophylactic excision of lymph nodes. In his series of 90 cases, 37 had local excision alone with a 5-year survival rate of 46%. Twenty-three had local excision plus dissection of regional lymph nodes within a period of 3 months, with a survival rate of 39%. Thirty had local excision plus delayed excision of lymph nodes, 3 months or longer after the first operation, with a rate of 40%[20].

McGovern. A survival rate for 5 years of 15.2%, determined in 99 out of 298 cases in his series, was reported by McGovern, in which local excision alone, or local excision plus removal of regional lymph nodes was performed[68].

Fanger and Roberts. These authors feel that more conservative therapy produces comparable results to radical surgery. In their series of 26 cases, they found that 7 patients survived 4 years or longer, even though they had either local recurrences or metastases treated following the initial surgery[35].

Discussion of Results. Wright, Clark and Milne, from Glasgow, speak of the generally accepted gloomy prognosis of malignant melanoma and then compare it to "such scourges as carcinoma of the bronchus or stomach" where the outlook is much less favorable. The cutaneous origin of malignant melanoma and its use of superficial lymphatic channels permit easy recognition in most cases, and to this might be added, the tendency, on many occasions, for the tumor to remain localized for relatively long periods of time.

In attempting to justify more radical therapy they mention, "If distant metastases appear without local recurrence, it is assumed, probably correctly, that the disease was already disseminated before the first excision was performed and that more radical initial treatment would have been unnecessary and unprofitable mutilation"[125].

It seems likely that final decisions about the best methods of treating malignant melanoma will have to await the arrival of comparable statistics. To this end the final section of this review, which follows, has been designed.

Recommendation. As has already been set up in the Commonwealth of Texas[21] and has been suggested by Wright, Clark and Milne[125], the first prerequisite to the cure of malignant melanoma seems to be the institution of a *Malignant Melanoma Registry,* perhaps even on an international basis. Because of the relative rarity of this disease, group methods of approach are necessary. Standardization of stain-

ing and sectioning techniques, of follow-up and statistics, of surgical procedures are required. Such an organization would be able to command grants-in-aid from government and philanthropic agencies, in a way that independent bodies could only hope for, and the approach to malignant melanoma from all sides, could be more quickly realized. The present day revival of interest in this disease, in its histogenesis, histopathology, histochemistry, comparative biology, ocular manifestations, and treatment, means only one thing, that it is a very "live subject."

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BOOK REVIEWS AND NOTICES

DIAGNOSIS AND TREATMENT OF THE ACUTE PHASE OF POLIOMYELITIS AND ITS COMPLICATIONS. Edited by ALBERT G. BOWER. University of Southern California. Pp. 250; 64 ills. Baltimore: Williams & Wilkins Co., 1954. Price, $6.50.

THIS book has been compiled by fourteen contributors, most of whom have worked together treating thousands of patients with acute poliomyelitis. The patients were chiefly cared for in the Los Angeles County Hospital. The report concisely details the methods which this group recommends for the management of poliomyelitis and its complications. The book would appear to be most useful for those who need specific information concerning the use of respirators, the care of tracheotomies, muscle tests, and the like. This manual should be most helpful to those whose experience with poliomyelitis has been limited.

R. H.

SPINAL EPIDURAL ANALGESIA. BY P. R. BROMAGE, M.B., B.S.(LOND.), F.S.A.R.C.S., D.A., Consultant Anesthetist, Chichester Hospital Group. Pp. 123; 41 ills. Baltimore: Williams & Wilkins Co., 1954. Price, $3.75.

THIS is the first textbook limited to the subject of epidural analgesia. The material presented is based upon the author's records of 1,000 personal administrations over a period of 5 years.

Dr. Bromage began his investigation of epidural analgesia as a reaction from the limitations of the relaxants techniques. He admits to the virtues of light general anesthesia and muscle relaxants, but feels that they contribute nothing to the solution of the problems of operative blood loss and postoperative analgesia and encumber the anesthetist with the treatment of paralytic apnea.

The author describes the anatomy and physiology of epidural analgesia very well. In addition to the very adequate description of the anatomy, the author has included several anatomical plates and schematic drawings which help one in understanding how analgesia may be produced by the introduction of local anesthetic agents into the epidural space.

Dr. Bromage describes completely the various techniques available for identifying the epidural space. He also presents by means of illustrations and tables, the drugs, equipment and dosage of drugs required for epidural analgesia. He devotes one chapter to the indications and contraindications for epidural analgesia, not only for surgery but also as an aid in diagnosis and therapeusis. As an Appendix, the author describes three accidents which had been encountered and points out the lesson to be learned from each case.

L. K.

CONNECTIVE TISSUE IN HEALTH AND DISEASE. Edited by G. ASBOE-HANSEN, University Institute of Medical Anatomy, Copenhagen. Pp. 321; 64 ills., 9 in color. Copenhagen: Ejnar Munksgaard, 1954. Price, $7.50.

THIS volume is a collection of twenty-three papers dealing with the anatomy, chemistry, physiology, and pathology of what is broadly termed "the connective tissue." The authors include the most prominent workers in this field from Denmark, Sweden, Finland, England, Italy, and the United States. It brings up-to-date the material presented in the 1950 Josiah Macy Conference on Metabolic Inter-relations and Randall's "Nature and Structure of Collagen" published in 1953. Because of the two preceding volumes on the same subject, it is more like a revision than a new edition.

An entirely new concept of the connective tissue system has been engendered in the past decade. This concept is of such fundamental importance in such a wide variety of disease states that it becomes imperative for every writer and teacher in the field of medicine to keep himself informed along this front. The book could hardly be intended for the busy physicians who are practicing the medicine of today but it is certainly essential for the men who are making the literature and the practitioners of tomorrow.

E. A.

NEW EDITIONS

Demonstrations of Operative Surgery. BY HAMILTON BAILEY, F.R.C.S., F.A.C.S., F.I.C.S., F.R.S.E., Emeritus Surgeon, Royal Northern Hospital, and Consulting General Surgeon, Metropolitan Ear, Nose and Throat Hospital, London; Hunterian Professor, Royal College of Surgeons of England. 2nd ed. Pp. 387; 538 ills. Lon-

don: E. & S. Livingstone, Ltd., 1954 (Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $6.00.

THIS book by Bailey and his collaborators is ably edited throughout by Doctor Bailey and is an interesting, readable, somewhat superficial resume of the common surgical procedures performed in a large London hospital. It should interest and enlighten the nurse, the medical student, and the general practitioner. The author has done well with this second edition. The book contains 538 excellent illustrations, some in color. It is well worth the price of $6.00.

G. R.

Textbook of Chiropody. BY MARGARET J. MCK. SWANSON, Cofounder of Edinburgh Foot Clinic and School of Chiropody. 2nd ed. Pp. 268; 160 ills. Baltimore: Williams & Wilkins Co., 1954. Price, $5.00.

THIS is an excellent volume dealing with a subject which is neglected by most practitioners. The importance of simple chiropodial conditions, the dangers involved in their neglect, and appropriate methods for their treatment are outlined in a thorough fashion.

C. S.

NEW BOOKS

Deprived Children. BY HILDA LEWIS, M.D., M.R.C.P. Pp. 163. New York: For the Nuffield Foundation by the Oxford University Press, 1954. Price, $1.55.

THIS book by an English psychiatrist describes the care and behavior of 500 children admitted to the experimental reception center at Mersham in Kent between 1947 and 1950. These children were admitted because of desertion, cruelty and neglect and showed neurotic behavior, maladjustment and delinquency. There are statistic and case histories to document the work and it all adds to the growing amount of literature which points up the importance of a stable home life with affection between parents and children as a basis for mentally healthy behavior. Highly recommended for the socially minded physician, social scientist and interested layman.

O. E.

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